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

**RUNNING HEAD: Management of stimulant-refractory 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 30th 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, tolerance, and not having the correct diagnosis. We finally consider the role of non-stimulants and combined pharmacological approaches. While the choice of medications 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 the choice of medications to the specific characteristics of the patient.

**KEY POINTS**

* Most patients with ADHD will respond to properly optimized stimulants
* 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, the possibility of tolerance, and lastly whether the diagnosis is correct.
* Currently, it is not possible to predict the response to ADHD medications

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 pharmacologic 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 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 SMD = 0.98 (95% CI: 0.44 to 1.51) on ADHD core symptoms and SMD= 0.57 (034 to 0.80) on symptoms of emotional lability in adults with ADHD [6]. Another meta-analysis of RCTs with ADHD medications found a standardized mean difference (SMD) = 0.30 (95% CI: 0.18 to 0.42) for methylphenidate (nine parallel-group RCTs), and SMD= 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].

1. **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 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 nonstimulant 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], that 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 Catala-Lopez 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 30th March 2021 (please see 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 ADHD core symptoms***

Coghill and Seth adapted the approach used in the MTA in terms of optimisation 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 optimisation 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 minimising 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 us of the pharmacokinetic and pharmacodynamic properties of the various stimulant formulations to optimise 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 behaviors [16]. Blader et al. [7] conducted a double-blind RCT assessing the comparative efficacy and tolerability of adjunctive risperidone, valproex sodium, or placebo for aggressive behaviors 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 case of non-response, had a second titration with the other stimulant class. The following algorithm was used: patients were started on 18 mg/d of methylphenidate Osmotic Release Oral System (OROS) with a titration of 18 mg increments until a maximum dose (72 mg/d) could be reached; however, clinicians could choose to titrate up to 90 mg/d 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/d, was used. Mixed amphetamine salts, up to 35 mg/d, was 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 nonstimulant medications are available for use when stimulants are not tolerated or yield suboptimal response

2.2.1 Food and Drug Administration (FDA)-approved nonstimulants

Nonstimulants approved by the 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 effect sizes for 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 to 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 *vs*. placebo compared to 6 RCTs for guanfacine, and only 1 RCT for clonidine *vs.* 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 Catala-Lopez et al. [10]are summarized in Table 1.

Viloxazine,is an unscheduled selective noradrenaline reuptake inhibitor with antagonistic activity at 5-HT2B and agonistic activity at 5-HT2C receptors[19]. It may also upregulate the levels of GABA-B receptors and have 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 extended-release 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 two weeks, and response at two 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 constituted the major nonstimulant 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 *vs.* 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 to 54.39, 3 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 confidence intervals (CI)- according to ratings by parents (SMD: -1.42, 95% CI -1.99 to -0.85, 2 RCTs), and teachers (SMD -0.97, 95% CI -1.66 to -0.28, 2 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 which is also an alternative, non-FDA approved, nonstimulant option for ADHD. There are multi-site studies in both children [26] and adults [27] with ADHD, so there is a reasonable 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 to 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, -1.07 to 0.43 and SMD = 0.24, -0.44 to 0.92, respectively). No significant differences, compared to placebo, were found for tolerability (OR= 1.51, 0.17 to 13.27) and acceptability (OR= 0.89, 0.21 to 3.74). In the Catala-Lopez et al. NMA [10], efficacy (treatment response: OR= 2.41, 95% CI = 0.48 to 11.63) and acceptability (OR: 1.54, 95% CI = 0.39 to 7.76)) were not significantly different than 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 (3 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 apnea/hypopnea 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 its 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 program 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 increased risk for Stevens-Johnson syndrome in the child and adolescent study [30], whilst a 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 nonapproved 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 medication is however meagre, and there few if any systematic controlled studies.

*2.2.2.5 Investigational compounds*

Several novel nonstimulant compounds have been trialled in RCTs over the last years. 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 *vs.* stimulants plus 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 vs 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 (ATMX) plus placebo for 4 weeks. Responders were continued on atomoxetine plus placebo. Non responders were randomized to atomoxetine plus methylphenidate or atomoxetine plus placebo for 6 weeks. After 1 week of combined treatment, scores of ADHD core symptoms (ADHDRS-IV-Parent: Inv total) were significantly lower in the ATMX+stimulants arm compared to the ATMX+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 XR*

In some countries (e.g., 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 GXR 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 the 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 (TEAEs) 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, and systolic and diastolic blood pressures while d-methylphenidate ER increased heart rate and 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 extended release added to stimulants was superior to stimulants plus 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 used of bupropion with stimulants. However, we mention it here because there is an evidence base for ADHD, and the extended-release formulation offers a pharmacokinetic profile that may translate into activity that covers the entire day. Bupropion is also likely to be used in combined treatment 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 behaviors refractory to stimulants in individuals with ADHD***

In the previously mentioned RCT (n= 175) by Blader et al. [7], children with aggressiveness refractory to optimized stimulant treatment presented with significantly greater reduction in the severity of aggression when treated with stimulants plus risperidone or (with slightly lower effect size) with stimulants plus divalproex sodium compared to stimulants vs placebo. These results extend those from a previous RCT [41] by the same group showing significant reduction of aggressive symptoms severity in children treated with optimized stimulants plus divalproex vs. optimized stimulants plus placebo. Another small RCT [42] of risperidone augmentation provided mixed findings, with positive results according to scores of aggressive behaviors 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 behaviors 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 vs stimulant+placebo on ADHD core symptoms, it did find significantly higher reduction of the severity of CD symptoms in the stimulants +clonidine arm.

1. **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 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 availability/license 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 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 extended-release clonidine 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 includes viloxazine [49], as this compound has only recently been approved by the FDA, and at the time of writing only in the US, 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 NMAs 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 Catala-Lopez 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 pharmacologic 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 optimisation of symptoms and response, but also maximal improvement in overall functioning as well as tolerability of treatment

1. **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 highligh three principles of good practice in clincial (psycho)pharamcology: 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 intial phase of the treatment, which decreases with an increased dose of medicaton- in this case, stopping or reducing the dose of the medication would prevent patients from receiving optimized doses of the medication; third, re-tritrating after a patient is reported to have experienced possible side effcts may be beneficial, since the presumed side effects may have been related to other cotemporaneous 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 which 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*). While we are not aware of single accepted definition of ‘adequate trial’ in this context 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.While we are not aware of 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/license doses 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 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 extended release 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 reflected 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. On 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 bid dosing, or a switch to an extended release formulation or changing time of administration, should be considered. With OROS methylphenidate, the issue may be of an under dosing 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, to other non-core but common symptoms such as emotional lability or other aspects of functioning often experienced as a complication or consequence ADHD. In clinical practice, it is not uncommon that parents or patients themselves complain of lack of efficacy of stimulants on symptoms/aspects (e.g., oppositional behavior, 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 behavior and hamper the response to stimulants. When present, co-occurring life events could benefit from appropriate supportive and psychological interventions, rather than additional medications for ADHD.

Additionally, the role of possible comorbities in mimicking or exacerbating ADHD symptoms should not be overlooked. For instance, individuals with comorbid learning disabilities (LD) may present with apparent attenuated reponse, 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 week-end 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, in which case an increased dose may be beneficial.

If none of these factors is considered to be a possible explanation for the lack of response to stimulants, then second 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 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 in combing stimulants and atomoxetine. Of note, combined use of atomoxetine together with drugs such as fluoxetine and paroxetine, which are also dependent on 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 alpha-2 agonists (clonidine and guanfacine), neuroleptics such as risperidone or aripiprazole or divalproex for the management of aggressive/oppositional behavior unresponsive to stimulants, and augmentation with alpha-2 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 of using additional agents in a substantial proportion of patients.

1. **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, then, if this is not successful, moving to second or third line pharmacologic options should be considered. Whilst the focus on non-pharmacologic 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 a more personalised, tailored, and efficient management of patients with ADHD.

**DECLARATIONS**

**Funding** N/A

**Conflicts of interest/Competing interests:** SC declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD. In the past year, JN is/has been an advisor and/or consultant for Adlon Therapeutics, Arbor, Eisai, NLS, OnDosis, Rhodes, Shire/Takeda, and Supernus. He was a DSMB member for Pfizer and Sunovion, and received research funds from Otsuka, Shire and Supernus. He also has received speaker fees from Shire/Takeda for disease-state presentations and served as a consultant for the US National Football League. DC has received research support from the National Health and Medical Research Council (Australia, NHMRC), research support and/or honoraria from Shire/Takeda, Medice, Servier and royalties from Oxford University Press and Cambridge University Press.

**Availability of data and material** N/A

**Code availability** N/A

**Authors' contributions: SC drafted the first version of the manuscript; JN and DC revised it critically. All authors read and approved the final version of the manuscript for submission and publication, and all agree to be accountable for the review.**

**Ethics approval** N/A

**Consent to participate** N/A

**Consent for publication** N/A

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

|  |  |
| --- | --- |
| **CORTESE ET AL. [12]** | **CATALA-LOPEZ 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 (0.68-1.07) |
| 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*

a *active medication better than placebo* b *active medication worse than placebo* c *pooling data for immediate and extended-release formulations*

CI: confidence interval; OR: odds ratio; SMD: standardized mean difference

**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** | **Arms/Dose** | **Duration (wk)** | **Key findings (efficacy)** |
| Guan | NCT00429273 [36] | 207 | 7-14 | Guan (1-3 mg/day)  d-methylphenidate  extended-release (DMPH) (5-20 mg/day) | 8 | Participants treated with COMB had significantly greater reductions in the 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 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 am (average: 3.3 ± 1 mg/day)  Stimulant + Guan-XR pm (average: 3.2 ± 1 mg/day)  Stimulant + placebo | 9 | At endpoint, Guan-XR arms showed significantly  greater improvement in the ADHD core symptoms severity (ADHD-RS-IV total scores) in the two Guan-XR arms compared to stimulants + placebo.  Both GXR arms showed greater improvement in the morning (GXR am: *p* = .019; Guan-XR pm, *p* < .001) and evening symptoms (Guan-XR am, *p* = .002;GXR pm, *p* < .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 the ADHD symptoms severity ADHD Rating Scale IV (ADHD-RS-IV) total score (*P=*.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 |
| ALC | NCT01099072 [57] | 40 | 7-13 | ALC (500-1500 mg/day)+MPH  MPH + placebo | 6 | No significative 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 son 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* < .696), Inattention (*p* < .429), or Hyperactivity-Impulsivity (*p* < .824) of the ADHD Rating Scale |
| 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 ADHDRS-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 years | 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). |
| Vitamin D | IRCT201404222394N10 [63] | 62 | 5-12 | MPH+vit D (2000IU)  MPH+placebo | 8 | No significant differences between the two study arms in ADHD core symptoms (Conners parents rating scale and ADHDS-RS) but significantly lower scores in the MPH+vit D on the Weekly Parent Ratings of Evening and Morning Behavior (WPREMB) |
| 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 on in the MPH+ zinc 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 |
| HX106 1 | 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 compared to the placebo group |

1: mixed herbal extract of *Gastrodia elata* Blume, *Liriope platyphylla* Wang et Tang, *Salvia miltiorrhiza* Bunge, and *Dimocarpus longan* Lour

ADHD: attention deficit hyperactivity disorder; ADHD-RS-IV: ADHD Rating Scale-IV; ALC: acetyl-L-carnitine; AMPH: amphetamines; Clon clonidine ; Clon-XR: clonidine extended release; COMB: combined; DMPH: d-methylphenidate extended-release; Guan-XR: Guanfacine XR ; Guan: guanfacine IR; K-ARS: Korean ADHD Rating Scale; MPH: methylphenidate; vit D: vitamin D

**Table 3. RCTs on the management of aggressiveness/oppositional behaviors refectory to stimulants in individuals with ADHD.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Compound** | **Registration id** | **N randomized** | **Age** | **Arms/Dose** | **Duration (wk)** | **Key findings (efficacy)** |
| RISP  DVPX | NCT00794625 [7] | 45 (refractory to stimulant optimization) | 6-12 | Stimulants+RISP  Stimulants+DVPX  Stimulants+Placebo | 8 | Greater reduction 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 (ES= 0.91) vs. Stimulants+Placebo |
| DVPX | NCT00228046 [41] | 30 | 6-13 | Stimulants+DVPX  Stimulants+Placebo | 8 | Significantly higher proportion of remitter s(for aggressive behavior in the Stimulants+DVPX  [57.14%]) vs. the stimulants+Placebo  [15.38%] arm (p<0.05). |
| RISP | NCT00297739 [42] | 25 | 7-12 | Stimulants+RISP  Stimulants+Placebo | 4 | 100% of the participants in the Stimulants+RISP  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 am  Stimulant + GXR pm Stimulant + placebo | 8 | Significantly greater reduction on the oppositional subscale of the Conner’s 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 + clonidine (0.1-0.2 mg/day)  Stimulants + placebo | 6 | 56% in the stimulants + clonidine 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 |

CLON: clonidine; DVPX: divalproex sodium; GXR: guanfacine extended release; RISP: risperidone

**Table 4. Recommendations on the management of ADHD from a selection of recent national/international guidelines (in alphabetical order). Recommendations on the hierarchy in the choice of medication are underscored.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 behavioral 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 behavioral classroom interventions (preferably both)  ***Adolescents 12-18 years***  FDA-approved medications. Training and/or behavioral interventions when available. | ***Pre-schoolers***  Psychosocial interventions  **Children/adolescents and adults**  Medications, in the following order:   1. long-acting stimulants 2. atomoxetine, guanfacine XR 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: 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-pharmacologic 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, with the following order 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 of 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. Pharmacologic options (with nor order specified): methylphenidate, lisdexamfetamine, guanfacine and atomoxetine  **Adults**  First line pharmacological treatment in moderate-to-severe cases. Psychosocial interventions or medications in mild cases |

AAP: American Academy of Pediatrics; CADDRA: Canadian ADHD Alliance Resource; CBT: cognitive behavioral therapy; CD: conduct disorder: NICE: National Institute for Health and Care Excellence; ODD: oppositional defiant disorder

**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 behavioral 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?

8. Is the diagnosis right?

* Consider second line medications (atomoxetine, guanfacine, clonidine)
* Consider augmenting agents (guanfacine or clonidine XR)
* Consider other agents under specialistic advice/supervision

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