Emerging challenges in ADHD pharmacotherapy research – outcome measures beyond symptom control and clinical trials

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SC conducted the literature search, DC and IW wrote the first draft, all other authors contributed to the writing and revision of the text.

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Search strategy and selection criteria:

We used the search strategy implemented in a recent network meta-analysis of ADHD medications[1] conducted on behalf of the European ADHD Guidelines Group. We used the studies included in and excluded from the network meta-analysis to allow us to identify the challenges of future research in pharmacological treatments of ADHD.

The following search terms were used for PubMed: ('Attention Deficit Disorder with Hyperactivity' (Mesh) OR adhd(tiab) OR hkd(tiab) OR addh(tiab) OR hyperkine*(tiab) OR 'attention deficit*'(tiab) OR hyper-activ*(tiab) OR hyperactiv*(tiab) OR overactive(tiab) OR inattentive(tiab) OR impulsiv*(tiab)) AND ('Amphetamines'(Mesh) OR 'Bupropion'(Mesh) OR 'Clonidine'(Mesh) OR 'Methylphenidate'(Mesh) OR 'Dexmethylphenidate'(Mesh) OR 'Guanfacine'(Mesh) OR Adderall(tiab) OR Amphetamine(tiab) OR Desoxyn*(tiab) OR Phenopromin(tiab) OR Amfetamine(tiab) OR Phenamine(tiab) OR Centramina(tiab) OR Fenamine(tiab) OR Levoamphetamine(tiab) OR Dexamfetamine(tiab) OR Dexamphetamine(tiab) OR Dexedrine(tiab) OR Dextroamphetamine(tiab) OR DextroStat(tiab) OR Oxydess(tiab) OR Methylamphetamine(tiab) OR Methylenedioxyamphetamine(tiab) OR Methamphetamine(tiab) OR Chloroamphetamine(tiab) OR Metamfetamine(tiab) OR Deoxyephedrine(tiab) OR Desoxyephedrine(tiab) OR Ecstasy(tiab) OR Atomoxetine(tiab) OR Biphentin(tiab) OR Bupropion(tiab) OR Amfebutamone(tiab) OR Zyntabac(tiab) OR Quomen(tiab) OR Wellbutrin(tiab) OR Zyban(tiab) OR Catapres*(tiab) OR Clonidine(tiab) OR Klofenil(tiab) OR Clofenil(tiab) OR Chlophazolin(tiab) OR Gemiton(tiab) OR Hemiton(tiab) OR Isoglaucon(tiab) OR Klofelin(tiab) OR Clopheline(tiab) OR Clofelin(tiab) OR Dixarit(tiab) OR Concerta(tiab) OR Daytrana(tiab) OR Methylphenidate(tiab) OR Equasym(tiab) OR Methylin(tiab) OR Tsentedrin(tiab) OR Centedrin(tiab) OR Phenidylate(tiab) OR Ritalin*(tiab) OR Duraclon(tiab) OR Elvanse(tiab) OR Focalin(tiab) OR Dexmethylphenidate(tiab) OR Guanfacine(tiab) OR Estulic(tiab) OR Tenex(tiab) OR Kapvay(tiab) OR Lisdexamfetamine(tiab) OR Vyvanse(tiab) OR Medikinet(tiab) OR Metadate(tiab) OR Modafinil(tiab) OR Nexiclon(tiab) OR Quillivant(tiab) OR Strattera(tiab)) AND (randomized controlled trial(pt) OR controlled clinical trial(pt) OR randomized(tiab) OR placebo(tiab) OR clinical trials as topic(mesh:noexp) OR randomly(tiab) OR trial(ti)) NOT (animals(mh) NOT humans(mh))

Unstructured abstract (max 150 words):
Although pharmacological treatments are recommended as a key component in the treatment of ADHD their use continues to spark intense debate. Despite considerable research effort there are still several gaps in our knowledge and several questions over the quality of evidence. Particular issues include uncertainty about long-term effectiveness and safety, safety profiles in adults and the comparative effectiveness of different medications. We focus on four key methodological issues for future research: 1) the use of appropriate trial designs; the need for 2) outcome measures targeting effectiveness beyond symptom control and 3) safety outcome measures; and 4) the application of clinical and administrative research databases to assess real-world outcomes. Potential solutions include: increased use of randomised placebo controlled withdrawal trials and large pharmacoepidemiological studies, using electronic healthcare records that address long-term effectiveness and safety of medications. Pragmatic head-to-head randomised trials to provide direct evidence on comparative effectiveness and safety profile.

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Although pharmacological treatments are recommended as a key component in the treatment of ADHD their use continues to spark intense debate. Despite considerable research effort there are still several gaps in our knowledge and several questions over the quality of evidence. Particular issues include: uncertainty about long-term effectiveness and safety; safety profiles in adults; and the comparative effectiveness of different medications. In this analysis we discuss four of the key issues required to improve research into and knowledge about, the use of medications in treating ADHD: 1) the use of appropriate trial designs; 2) the need to use a) broader outcome measures that inform on effectiveness beyond symptom control and b) safety outcome measures; and 3) the application of clinical and administrative research databases to assess real-world outcomes. The aim is to set out those issues that need to be addressed, make initial suggestions about how this can be achieved and stimulate debate about how we can develop research approaches that will improve clinical understanding and decision making.

Attention-Deficit/Hyperactivity Disorder (ADHD), as defined in the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* (DSM-5)[2], is characterised by age-inappropriate and impairing levels of inattention and/or hyperactivity-impulsivity. Hyperkinetic disorder, as per the *International Classification of Diseases-10th edition* (ICD-10)[3], is a more restrictive syndrome, requiring symptoms and impairment in both the inattention and hyperactivity-impulsivity domains. ADHD is one of the most commonly diagnosed neurodevelopmental disorders, with an estimated worldwide prevalence of 5%[4] in school-age children. Impairing ADHD symptoms persist into adulthood in around 65% of cases[5]. There is emerging evidence that ADHD often persists into older adulthood (> 55 years) and that when it does it is frequently accompanied by similar comorbidities such as anxiety and depression, and social impairment as in younger age groups [6,7].

Interventions for ADHD include both pharmacological and non-pharmacological approaches. Licensed medications for ADHD comprise psychostimulants (e.g., methylphenidate and amphetamines) and non-psychostimulant drugs (e.g., atomoxetine and the alpha-2 agonists, clonidine and guanfacine). Parent training/behavioural interventions, dietary interventions, cognitive training and neurofeedback, among others, have been suggested as non-pharmacological options for treating ADHD. The role, positioning and balance between non-pharmacological and pharmacological treatments varies across international evidence-based clinical guidelines (Table 1).

Whilst recent meta-analytic studies have not supported the efficacy of psychological therapies for reducing core symptoms of ADHD (i.e., inattention, hyperactivity and impulsivity) when considering outcomes rated by probably blinded assessors,[8-10] some non-pharmacological interventions appear effective at improving associated features (e.g., parent training for oppositional/conduct problems or cognitive training for working memory deficits). This analysis focuses on pharmacological treatments for ADHD for which there is considerable evidence for short term efficacy and safety[1] and the use of medication for treating ADHD is supported by all major evidence-based guidelines (Table 1). However there are still several unanswered questions about the comparative and long-term efficacy and safety of ADHD medications, and their effectiveness in day to day clinical practice and for special populations that are typically excluded from trials. Although there are several countries, such as Germany, where the prescription of pharmacological treatments for ADHD has dropped over recent years there are also many (USA, UK, Australia and Hong Kong) where rates continue to rise in children, adolescents and adults [11]. As there is not yet a consensus about what proportion of those with ADHD should be treated with medications this continues to spark intense debate[12-15]. There is also considerable between country variation in rates of prescribing with recent data from 150 million individuals in 14 countries showing that in 2010 ADHD medication prevalence varied between 0·27 and 6·69 per 100 children and adolescents (aged 3-18) and between 0·003 and 1·48 per 100 adults (over 18 years) [11]. Whilst

we urgently need to fill in the important gaps in our knowledge to do this effectively will require several adjustments in trial methodology and an openness to collaborative interdisciplinary work that combines different designs and approaches. We will now discuss the four key methodological issues that we believe are the most important first steps on this journey.

The use of appropriate trial design

Randomised controlled trials (RCTs) remain the gold standard in the evaluation of efficacy. However, care must be taken both in the design and interpretation of RCTs. Some ADHD studies have employed "enrichment methodologies" for instance including an initial open label phase to identify responders and then only randomising these responders into the main RCT phase.[1] Whilst this may be helpful when studying the long-term effects of treatment the use of enrichment in short term efficacy studies (usually around 12 weeks) can over-estimate the treatment effect and underestimate adverse effects. Interpretation of the findings from these enrichment trials is complex and not straightforward; hence we do not encourage the use of this design to examine short-term efficacy and adverse effects.

While placebo-controlled trials are particularly useful in the evaluation of efficacy, they are less helpful in guiding daily practice where a range of pharmacological treatments are available. Network meta-analyses provide estimation of the comparative efficacy and tolerability of two or more interventions, even when they have not been investigated head-to-head in randomised controlled trials. However, a recent network meta-analysis on ADHD medications found that the majority of indirect comparisons were of low or very low quality[1]. Thus, more high quality head-to-head trials are urgently needed. Whilst head-to-head comparison studies of different active treatments are suitable to assess the comparative efficacy/tolerability of two or more active compounds, these should be combined with more pragmatic designs that retain both a randomised allocation to treatment and appropriate comparison group whilst allowing for dose optimisation for

each treatment arm. This way the findings are more useful for translation, better able to inform guideline developers and, most importantly, day-to-day clinical practice. The lack of such trials in ADHD leads to continuing uncertainty about the relative clinical and cost effectiveness of the various ADHD medications for people who have not previously been treated with medication, or the various prescribing strategies that can be employed when monotherapy has failed. [16] There is considerable inter individual variability in response to ADHD medications and a more modest but clinically important goal of these direct head-to-head comparisons is to generate evidence about which treatment is potentially most applicable to which subgroup of patients.

The long-term efficacy of many ADHD medications also remains unclear. [17] Conducting long-term placebo-controlled trials that withhold effective treatments from patients for long periods of time is impractical and ethically questionable by patients, professionals and ethics committees. We agree with NICE [18] and EMA[19] recommendations for placebo-controlled withdrawal trials in ADHD; however these trials are expensive, particularly with off-patent medications, and we urge funding agencies to support such trials.

An important and topical area for research development, particularly under-developed in medicines for children [20], is the field of personalised and precision approaches to treatment. NHS England defines it as 'a move away from a 'one size fits all' approach to the treatment and care of patients with a particular condition, to one which uses new approaches to better manage patients' health and target therapies to achieve the best outcomes in the management of a patient's disease or predisposition to disease'. In physical medicine this most commonly refers to the use of biomarker, particularly genomics, to establish ways of predicting what works for whom. Whilst this is just as relevant in psychiatry in general and ADHD more specifically complex aetiologies, causal heterogeneity and a lack of reliable biomarkers make the task much more complex. However consideration of broader classes of biomarkers including cognitive and neurophysiological

measures will hopefully pay dividends [21]. It will be equally important and clinically relevant to identify approaches that can enhance treatment optimisation and adherence, and combine pharmacological and non-pharmacological treatments more effectively. Whilst the definitive evidence to guide clinical decision making around a truly individualised approach to care is currently lacking recent evidence suggests that it is possible to improve and optimize overall clinical outcomes at a group level within real world clinical settings [22] and that the key to this may be closer monitoring and an increased use of routine outcome measures. Ongoing studies into stepped care approaches to care will inform whether the delivery of adaptive multimodal treatment strategies in routine care can improve clinical outcomes and advance the field (e.g. [23,24]). Another important issue is how to translate personalised medicine research into clinical practice. As atomoxetine is metabolised by cytochrome P450 2D6 (CYP2D6), theoretically, slow metabolisers will be more likely to experience adverse effects than normal or fast metabolisers. Whilst Michelson et al [25]confirmed this to be the case there are not yet any studies to assess the effectiveness of CYP2D6 testing in real-life clinical practice. The company prescribing material for atomoxetine recommends prescribers to consider dose adjustment if they know the patients are slower metabolisers [26]. However, the prescribing material does not recommend CYP2D6 genotyping prior to the initiation of atomoxetine and genotyping is not routinely available, or funded, and published evidence based guidelines have not yet given any advice on this matter [20]. Consequently, there is a breakdown in theoretical application of personalised medicines and real-life practice, indeed none of the members of the European ADHD Guideline test their patients prior to initiation of atomoxetine.

Classic clinical trials, particularly those in psychiatry, are currently extremely expensive and require labour-intensive approaches to data collection. We recommend the exploration and development of approaches to data collection that include objective measures and patient-reported outcomes and take advantage of new digital technologies. These new approaches have the potential to allow more efficient monitoring across the day and over the long-term, whilst significantly reducing the cost of

clinical studies. The ability to collect repeated longitudinal "real time" data from individual patients through phones, wearables and over the internet has the potential to significantly improve clinical measurement in ADHD although this research is still in its infancy.[27] One example is the potential for the use of ecological momentary assessments to make real time assessments of ADHD symptoms, emotional lability, life quality and a wide range of other emotions and mental states. Ecological momentary assessments involves a repeated sampling of subjects' current behaviours and experiences in real time, in their own natural environments [28]. The aim is to minimize recall bias, maximize ecological validity, and allow study of the micro-processes that influence behaviour in a real-world context. Another is the potential for actigraphy to assist in the objective evaluation of motor hyperactivity and response to medication across the day. One area of particular interest is the management of adverse events, where experience from physical medicine could be adapted to track medication related changes in blood pressure, heart rate, sleep disturbance as well as symptom change across the day.[29] Both clinicians and researchers would be able to make use of these data to plan treatment, give advice about the need for treatment and develop new strategies for treatment optimisation. Many ethical, methodological and practical issues need to be considered and addressed in order to harness the full potential of digital technology but work is ongoing[29]. Table 2 shows some of the methodological research topics we believe are required to move the field on in a meaningful way.

Measures of effectiveness that move beyond core symptom control

ADHD has a profound impact on many aspects of day-to-day life and patients with ADHD have significantly worse educational, economic, medical and social outcomes. These include increased risk of drug use/addictive behaviours, antisocial behaviour, poor academic and occupational outcomes, reduced social functioning, low self-esteem, and increases in driving accidents and offences, health and social service use and obesity.[30]

Despite this current clinical trials, both pharmacological and non-pharmacological, continue to focus on reductions in core ADHD symptoms as the primary, and often only, measure of efficacy. We strongly suggest that, to facilitate a more comprehensive understanding the positive and negative impacts of ADHD treatments, a much broader range of outcome measures into clinical trials and day-to-day clinical practice (Table 3). Whilst we endorse the use of these measures in future trials we also that there is considerable scope for improvement in the measures used currently to assess functional outcomes and quality of life. Whilst there is a need to validate measures for older adults it is an issue across all age groups [31].

Most of the recent pharmacological trials have been industry-funded studies conducted as part of a formal regulatory process, the explicit purpose being to generate the evidence required to support labelling claims and licensing applications. For these studies, the regulatory agencies typically require change in core ADHD symptoms as the primary outcome measure. Whilst safety and tolerability also need to be demonstrated, it is only since 2010 that companies in Europe have been required by the European Medicines Agency (EMA) to present additional data to support improvements in broader functional outcomes and quality-of-life.[19] In the US, these broader outcome data are still not required by the Food and Drugs Administration (FDA).

Whilst data from several industry-sponsored studies do support a positive impact of ADHD medications on quality of life and functional impairments,[32-34] more data are required. Clinically, it is apparent that optimal symptom reduction is not always associated with normalisation of quality-of-life and social functioning. This is supported by recent studies showing that these different approaches to assessment (i.e., symptom reduction, improved quality-of-life, and reduction in functional impairment) capture distinct but interconnected aspects of treatment response.[35,36] Again, further studies investigating these clinically important relationships are required.[37]

Another consequence of the regulators' requirement for a disorder-specific symptom focus to outcome measurement is that other potentially important outcomes, such as improvement in specific aspects of neuro-cognition, are ignored. Therefore, despite considerable evidence to indicate that ADHD is associated with impairments across a broad range of cognitive domains, [38] very few large-scale studies have included robust cognitive measures. The significance of this limitation is highlighted by evidence that ADHD medications can result in significant and potentially clinically important improvements in several aspects of cognitive functioning,[39] and that these improvements can occur independently of medication-related changes in ADHD symptoms.[40] There is also, of course, the possibility that ADHD medications could themselves result in impairments in cognitive functioning and whilst the EMA has indicated that new ADHD medications should test for cognitive adverse effects in post-marketing long-term studies, as far as we are aware of only one such study has been published so far [41]. For this type of study we would recommend the use of well-defined and validated batteries of tasks with known neuroanatomical and neuropsychopharmacological associations such as the CANTAB battery [42] rather than questionnaire measures like the BRIEF [43]which measure constructs with high levels of overlap with symptoms and therefore add less to the assessment. An important focus of future studies should be to investigate whether partitioning patients on baseline cognitive performance can predict differential treatment responses that would then allow clinicians to select the most appropriate treatment for individuals with a specific cognitive profile.[37]

As ADHD is a chronic disorder with symptoms and impairments that frequently continue into adulthood,[5] it is particularly problematic that most treatment studies focus on the short term with a general lack of long-term studies. Observational studies of long-term outcomes have reported rather disappointing results in terms of symptom control and high-quality data on functional outcomes are relatively sparse. The influential Multimodal Treatment of ADHD (MTA) study initially reported very positive outcomes for a carefully controlled medication protocol delivered during the 14-

month RCT.[44] However when the authors compared naturalistic symptom outcomes at 12 – 16 years post randomisation between those who, over the first 10 years of the study, had negligible, inconsistent or consistent exposure to ADHD medication, they did not find any differences between these groups. [45] It is not possible to tell from these data whether ADHD medications lose their effects over time, or whether these outcomes reflect the need to continue with a more rigorous approach to monitoring and treatment adjustment similar to that delivered during the first fourteen months of the trial. Recently published prospectively collected data from a clinical ADHD treatment pathway modelled on the MTA protocols reported more positive results, which suggest that, if carefully managed, ADHD medication treatment can result in positive and persisting long-term effectiveness, very similar to the 14-month treatment effects reported for the medication arms of the MTA study.[22]

This lack of evidence about longer term outcomes has been recognised by the regulatory authorities and the EMA has introduced a requirement that companies must report longer term follow-up data as part of the registration process for all new ADHD medications.[19] Consequently, several longer-term randomised placebo-controlled treatment withdrawal studies (where an effective medication is either continued or withdrawn and replaced by placebo) assessing longer-term efficacy in children, adolescents, and adults have now been published.[46] Taken together, these studies generally support continued efficacy, at least up to 6 months or a year, but don't really answer the question about true long term effects. They also suggest differences between the drug classes with faster and more consistent relapse in the stimulants compared to the non-stimulants and with a more rapid rate of relapse for guanfacine compared to atomoxetine. It is not yet clear whether these differences reflect variations in mechanisms of action and persistence of the medication effect or alternatively, whether they are simply due to differences in study design and definitions of response and relapse. It is also not yet clear which other factors (e.g. temperament, comorbidities, family and other environmental factors) in addition to the pharmacological effects of the medication and the way that treatment is

monitored and adjusted impact on the course of response over time. Clearly, more methodologically sophisticated and sound research is needed to establish the most appropriate outcome measures and definitions to accurately and comprehensively evaluate the long-term effectiveness of different pharmacological treatments.

Safety outcome measures

Our recent data have shown that ADHD medication prevalence in 2010 (per 100 children aged 3-18) varied across 14 countries from between 0·27 to 6·69 of children and adolescents. [11] As some of these patients will remain on treatment for several years, the longer-term safety and tolerability issue of these medications must be addressed.

Stimulants and atomoxetine may increase blood pressure and pulse rate due to their effects on the sympathetic nervous system. In the majority of patients, these relatively small increases of blood pressure and pulse rate are unlikely to cause serious harm.[47] However, an increased relative risk of myocardial infarction and arrhythmias in the early period after the start of methylphenidate treatment was reported in one study[48] albeit not replicated in others.[49] A causal association has not been confirmed, however even if one exists, the absolute excessive risk is very low. Further research to monitor and evaluate the cardiovascular risks and effects of these medications before, during treatment, and after treatment cessation is still needed. Currently, the majority of published research is on children and adolescents treated with stimulant medications (mainly methylphenidate and amphetamines). In comparison to stimulants, far fewer safety/tolerability data are available for the non-stimulant ADHD medications drugs (such as atomoxetine, clonidine and guanfacine); hence we recommend further long-term studies focussing on these new drugs. Previously, systematic observational studies have mainly focused on the risks for sudden death, growth and cardiovascular effects. There are however several other potentially important adverse outcomes including metabolic, psychiatric and neurological difficulties. Furthermore, in some children, as well as adults, polypharmacy with antipsychotic and antidepressant drugs, are used to control various non-

core symptoms and co-morbidities. The prescribing prevalence, risk and benefit of co-prescription of other psychotropic drugs are still poorly understood. Finally, increasing numbers of adults are receiving ADHD medications.[50] These older patients may have adverse event profiles different to those seen in children, but currently, there are few data describing the adverse effects of ADHD treatment in this patient group. A recently published study found increased risk of diseases of the basal ganglia and cerebellum in patients with a history of attention-deficit/hyperactivity disorder [51]. Although there is no robust evidence to show that medications are associated with this increase in risk, it is important to continue to monitor potential neurological adverse effects in older patients.

Application of clinical and research databases for real-world outcomes

While placebo-controlled clinical trials are particularly useful in the evaluation of efficacy, they are less helpful in studying adverse events and other real-world outcomes. Studies with large databases are currently the most viable option to monitor rare adverse events, long-term safety/tolerability and other real-world outcomes of ADHD medications. Whilst observational studies have their own limitations such as the potential for selection biases, misdiagnosis and non-adherence to treatment, they have a key strength with regards to the potential for large sample sizes and in the richness of the available data. In recent years, several self-controlled methods have been developed such as self-controlled case series.[52] These studies are designed to make comparisons within the same subject during times that they are on and off medication. They have advantages over traditional cohort and case-control studies as they remove the effects of time-invariant confounders (e.g., genetic influences)[52] and significantly reduce the problem of confounding by indication. Analyses of data from several large-scale databases that link key ADHD-related community treatment data with other key health, academic and social outcomes have demonstrated associations between medication administration and real world outcomes such as reductions in criminal behaviours,[53] trauma-related emergency room visits,[54] and motor vehicle accidents[55], better performance on academic tests,[56] without increased risk of psychosis[57] or suicidal attempt.[58] Notwithstanding the

methodological challenges, careful analysis of accurately ascertained and linked large-scale data in health, education, and social care and criminal justice systems provides an important avenue of research. To date almost all studies have utilized data from only one country and only one database. We recommend the application of meta-analyses [59-61] and/or mega analysis of multinational database [11] studies to examine the external validity and generalisability of results of pharmacoepidemiological studies. It is encouraging to see that many research groups have already started to use large database approaches in ADHD research; however increased collaboration between these groups should be fostered and encouraged, particularly in the development of new methodological research approaches such as the combination of data from different databases into mega-studies with the power to identify rare adverse events. The European ADHD Guidelines Group is working to coordinate the work of several international groups and develop strategies for multinational studies.

It is also very important to recognise the inherent limitations of these large registry and database studies. They do not usually collect psychometrically validated and reliable outcome measures or include an un-medicated ADHD comparison group. Therefore, in some circumstances prospective ad hoc studies are needed. These prospective studies are usually more difficult and expensive to conduct. The European Commission-funded ADDUCE study has just completed. ADDUCE is a large prospective observational study into the long term adverse effects of methylphenidate with both untreated ADHD and healthy controls. ADDUCE collected structured and validated outcome measures which can complement the results from large database studies (see Inglis SK et al BMJ open 2016; 6(4): e010433 for protocol). Further, methodological development of prospective observational studies are required and should be encouraged. A combination of routine healthcare data collection and ad hoc data collection can be developed and should be a priority of this type methodological research.

Conclusions

We recommend the development of clearer guidance to support and encourage work across these four aspects of research methodology. Whilst all are feasible in order for them to be realised researchers will need to be prepared to take risks and funders will be required to accept these risks. The regulators also need to recognise the gaps in knowledge and work with industry to ensure that they contribute to advancing the field. This work has started and the changes in emphasis by the FDA and EMA away from an over reliance on short term efficacy and safety have already resulted in the development and adoption new study designs. We support the model successfully developed by the EMA (European Networks for Paediatric Research at the EMA – ENPR-EMA) to promote interaction between academic researchers, industry and clinical research organizations to develop a more integrated approach to drug development and clinical trials but would add into this mix the need for National research funders to join this effort as they, with their non-commercial approach to research, have the opportunity to provide the much needed last piece of the puzzle.

Table 1. Summary of treatment recommendations in key national ADHD guidelines.

	2018 NICE [a]	2018 German guidelines [b]	2014 BAP [c]	2011 ENAA [d]	2018 CADDRA [e]	2011 AAP [f]	2007 AACAP [g]
Pre-school children	*Children under 5 years:* • First-line treatment: ADHD-focused group parent-training programme • If ADHD symptoms still impairing across more than one domain: obtain specialist advice	*Children under 6 years:* • Psychoeducation + • First-line treatment: ADHD-focused parent-training programme at home (based on cognitive behavioural therapy (CBT), individual or group setting); ADHD-focused education training/programme for kindergarten teacher; individual or group setting • If ADHD symptoms still impairing across more than one domain: obtain specialist advice (medication as possible option for children > age 3)	Not discussed	Not discussed	Not discussed	*Children aged 4-5:* • First line: Teacher/parent administered behaviour therapy • Methylphenidate if behaviour therapy not effective and persistence of moderate-to-severe impairment	*Children aged 3-5:* No specific recommendations but guidelines note that medication should be used with cautious titration

School-age children and adolescents	*Children and young people 5 years and over:*
	• Environmental modification.
	• If persistent significant impairment in at least one domain of life: medication (order of preference: 1) methylphenidate, 2)lisdexamfetamine, (consider dexamphetamine if lisdexamfetamine not well tolerated), 3) atomoxetine or guanfacine)
	• If comorbid oppositional defiant disorder or conduct disorder: add in a parent training programme
	• For adolescents: If symptoms still impairing in at least
		Children and young people 6 years and over:
		• Psychoeducation +
		If mild to moderate:
		• First-line treatment:
		  • parent management training / family-based interventions; complementary patient-based interventions if needed
		  • interventions at school / workplace; complementary patient-based interventions if needed
		• If still persistent significant impairment: medication (order of preference: 1) stimulants, 2) atomoxetine or guanfacine)
		If moderate to severe:
		• medication (order of preference: 1) stimulants, 2) atomoxetine or guanfacine)
		• If still persistent significant
			Children with severe ADHD or moderate ADHD non-responsive to psychological treatments:
			• psychostimulants
			If risk of misuse of psychostimulants by children or the adults supporting the child:
			• atomoxetine
				Not discussed	First line: Long-acting preparations (amphetamine mixed salts, methylphenidate, lisdexamfetamine)
					
					Second line/adjunctive: long acting preparations (atomoxetine and, for children 6-12 y only, guanfacine XR)
					
					Second line/adjunctive: short-acting and intermediate acting preparations: dextro-amphetamine sulphate, methylphenidate)
						Children aged 6-11:
						• Food and Drug Administration (FDA)-approved agents (order: stimulants, atomoxetine, extended release guanfacine, extended release clonidine), and/or evidence based teacher/parent administered behavior therapy (preferably both)
						Adolescents (12-18 years):
						• FDA agent, and possibly behavioural therapy (preferably both)
							Children aged 6-12 and adolescents aged 13-17:
							• Initial treatment: FDA-approved medication (usually stimulants first line; atomoxetine first line if comorbid substance use disorder, anxiety, tics)
							• If FDA-approved medication not effective: review case and then consider behavior therapy and/or agents not approved by the FDA
							• If comorbid disorders or stressors in family life: psychosocial treatment
							Behavioural approaches: first-line when mild ADHD symptoms and minimal impairment, unclear diagnosis, or if parents refuse pharmacological treatment

	one domain of life after medication treatment: cognitive behavioural therapy	impairment: parent management training / family-based interventions; complementary patient-based interventions if needed • interventions at school / workplace; complementary patient-based interventions if needed For patients with ADHD + substance use disorder, ADHD + Tics: no preference for stimulants over atomoxetine, guanfacine For patients with ADHD + anxiety: no preference for stimulants over atomoxetine					
Adults	• First line: medication (order of preference: 1) lisdexamfetamine (consider dexamphetamine if lisdexamfetamine not well tolerated) or methylphenidate; 2) atomoxetine;) • Non-pharmacological treatment if patient's choice, difficulty adhering to medication, medication ineffective or not tolerated	• Psychoeducation + • First line: medication • Non-pharmacological treatment if patient's choice, difficulty adhering to medication, medication ineffective or not tolerated	Stimulants are first-line treatment Atomoxetine as first-line treatment in patients with comorbid substance use disorders	Psychostimulants: first line Atomoxetine; second line Bupropion, guanfacine, modafinil and tricyclic antidepressants: third line Note: The first-line medications remain the treatment of choice for older adults when their medical condition permits their use.	First line: Long-acting preparations (amphetamine mixed salts, methylphenidate, lisdexamfetamine) Second line/adjunctive: long acting preparations (atomoxetine) Second line/adjunctive: short-acting and intermediate acting preparations: dextro-amphetamine sulphate, methylphenidate)	Not discussed	Not discussed

[a] National Institute for Health and Care Excellence. 2018, available at https://www.nice.org.uk/guidance/ng87 [16] (accessed on 16/07/2018)
[b] Draft provided by the German Guidelines Committee (https://www.awmf.org/uploads/tx_szleitlinien/028-045l_S3_ADHS_2018-06.pdf)
[c] British Association of Psychopharmacology. [62]
[d] Kooij et al. 2010. [63]
[e] Canadian ADHD Resource Alliance, available at https://caddra.ca/pdfs/caddraGuidelines2011Chapter07.pdf (accessed on 16/07/2018)
[f] American Academy of Pediatrics. [64]
[g] American Academy of Child and Adolescent Psychiatry. [65]

Table 2. Methodological research topics

Methodological research:

- Randomised withdrawal study
- Pragmatic trials:
  - Head to Head comparison of different pharmacological treatments
  - Treatment pathway
  - Personalised treatments and stepped care approaches
  - Combination of pharmacological and non-pharmacological treatments
- Novel approaches to data collection and analyses:
  - The application of routine data for safety monitoring
  - The application of methods using longitudinal within patient data analyses such as self-control case series
  - The combination of big data from different countries
  - The use of real time individual patient for clinical management and dose optimization
- The development of standardised approaches to define response and remission including validation of common outcome measures using the approach of Jacobson and Truax and the concept of minimally important clinical difference (MICD)

Table 3: Broader outcome measures for assessing efficacy/effectiveness and tolerability/safety of ADHD treatments.

- Core ADHD symptoms
  - Rating scales/semi-structured interviews with multiple raters (patient/carer/teacher/clinician)
  - Observations in classroom or test situations
  - Objective measures (e.g., actigraphy and other wearables)
  - Real time and momentary sampling through the use of mobile technologies and apps
- Measures of associated symptoms and disorders
  - Concurrent symptoms (e.g., emotional lability, mind wandering)
  - Comorbid psychiatric disorders (e.g., depression, anxiety and oppositional defiant disorder)
  - Substance misuse/abuse
- Functional impairments
  - Global functioning [e.g., Clinical Global Impressions – Severity (CGI-S) and Improvement CGI-I); Children's Global Assessment of Functioning (CGAS); Columbia Impairment Scale]
  - ADHD specific measures [e.g., Weiss Functional Impairment Rating Scale-Parent Report (WFIRS-P); ADHD Impact Module (AIM)]
- Cognition
  - Core cognitive characteristics e.g. working memory, response inhibition, decision making, attention, variability
  - Motivational and emotional characteristics, e.g. reward processing
  - Academic performance and attainments
- Long-term effectiveness outcome measures
- Quality of Life (self- and proxy-rated)
- Family and relationship functioning
- Grade progression, academic outcomes and employment status
- Criminal activity
- Driving and pedestrian behaviours and violations (real-life and simulated)
- Other health-related behaviours (e.g., accidents and visits to emergency departments)
- Long- and short-term safety and adverse events
  - Cardiovascular events
  - Neurological events
  - Psychiatric events (including suicidality)
  - Growth
  - Adverse effect associate with polypharmacy of psychotropic drugs

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