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The management of Paediatric ADHD – Bringing evidence to the clinic  
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| Funding Information:        | ADHD is the most common neurodevelopmental disorder presenting to child and adolescent mental health and developmental paediatric services. While ADHD presents with a spectrum of severity, co-occurring conditions and adverse outcomes, many individuals experience significant negative outcomes due to ADHD, both during childhood and into adolescence and adult years, with a high financial cost to society and impact on well-being and quality of life. This makes timely and effective intervention for core ADHD symptoms and co-occurring problems a high priority for healthcare and society more widely. Much research has reported on the benefits and adverse effects of different interventions for ADHD, both pharmacological and non- |
| Abstract:                  |                                                                                                |
pharmacological. These individual reports and the meta-analyses summarizing the findings are sometimes inconsistent and difficult to interpret, making it hard for clinicians to synthesize research and implement the findings in everyday care. Here we provide an up-to-date summary of the current evidence on the main domains used for intervention for children and adolescence with ADHD, alongside a description of the key methodological challenges and how they may influence results. We summarize international guidelines, highlighting the common principles and the reasons for divergence, where these occur. We discuss the application of evidence-based practice in an individualised context, to achieve optimal outcomes that prioritise individual strengths and impairments, as well as the personal treatment targets of children and their families. Finally, we consider how access to care for this common and impairing disorder can be improved in different healthcare systems.

Response to Reviewers:

Wednesday, 28 July 2021

Dear Dr Roessner, Dear Veit

Ms. No. ECAP-D-21-00277
The management of Paediatric ADHD – Bringing evidence to the

We thank you and the reviewers for your helpful comments on the above manuscript and the opportunity for us to revise and resubmit. Below we describe the changes we have made in relation to these comments.

We first highlight that we have changed the title to: The management of ADHD in children and adolescents – Bringing evidence to the clinic. The change reflects our desire to avoid an inaccurate use of the word ‘paediatric’, which we thought might be confusing to some readers in suggesting the issues discussed in this paper were pertinent only to paediatricians.

Reviewer #1: This is a well written review that will be quite useful to providers. The strengths are the synthesis of decades of research across disciplines and countries, and the highlighting of important commonalities and reasons for minor discrepancies when they occur. The discussion of blinding and ascertainment biases and impact on different interventions is excellent, as are the summary panels.

A few minor points:

In the abstract it is noted that ADHD is treated by mental health and developmental pediatric providers. Developmental pediatrics is a subspecialty field, but in the US for example, the majority of ADHD medications are managed by pediatricians or primary care physicians. This might be a cultural difference in health care but would suggest specialist mental health and pediatrician or primary care provider.

This issue was identified by both reviewers, and we thank them as we agree it is important to discuss and demonstrate European – North American differences. To do so, we have added a row in Table 4 on the different guidelines’ recommendations for who can diagnose and prescribe for ADHD. We also discuss these differences in the text, p 15, lines 42-46).

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We have removed the word ‘disabling’. (We recognize that ADHD is a wide spectrum and that cultural/country differences in recognition are significant.)

Reviewer #2: This manuscript reviews the evidence about the effectiveness and safety of treatments for children with ADHD for the purpose of informing clinical care. In addition to considering the actual evidence, the authors critically discuss the research...
methodology that was used to generate the evidence, and identify important limitations, such as the dearth of controlled studies on the long-term effects of treatment.

The main strength of the paper is the critical appraisal of the research methods, which provides insight into the quality and shortcomings of the available data (pages 13-19). The paper is clearly written and easy to follow, with informative tables that summarize the findings. Of special value is the comparison between the most important practice guidelines.

There are a few weaknesses:

1. The abstract provides little information, being a rather general statement of what the paper tries to achieve, but without offering any conclusion about the main findings of the review.

The Abstract has been entirely re-written to reflect this comment and provide more specific information (at a high level) for the reader.

2. The introduction does not provide a persuasive rationale for writing still another review of ADHD treatments when there have been many systematic reviews and meta-analyses. The paper in fact makes some new contributions in terms of critical discussion of the evidence, comparison of practice guidelines, and general synthesis of treatments, but these could be better highlighted.

We have extensively re-written the Introduction based on this helpful feedback. It now gives a briefer, but we think important, overview of ADHD and then highlights the key issues we will address.

3. One of the stated aims is to turn the results of randomized clinical trials into personalized approaches, but this does not seem to have been adequately developed in clearly implementable steps. Some recommendations sound obvious and rather non-specific (e.g., page 27, lines 3-13, “It is important to ensure that patient and parental priorities, preferences and choices are taken into account etc…” One could say that such considerations apply to any good clinical management.

We have removed the aim of a personalise treatment approach from the manuscript. While this is an ultimate aim, the authors do not think there is currently sufficient evidence to undertake a personalised approach to care in the sense highlighted above. We have, however, retained the section on management and tailoring to the individual patient and family. While, at one level we agree with the reviewer that some of this is generic, our observation is that hard-pressed clinicians often forget to implement these important principles in practice and may over-focus on group-level recommendations, which may not meet patient needs.

4. On page 24, lines 8-9, it is stated that "all guidelines agree that medications should be initiated by ADHD specialists". It all depends on what is the definition of "ADHD specialist". In the U.S., stimulant medication is often initiated by pediatricians. Can a pediatrician be an ADHD specialist? Does it require special training to achieve that qualification?

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Emily Simonoff
Chair, European ADHD Guidelines Group
The management of ADHD in children and adolescents – Bringing evidence to the clinic

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Conflicts of Interest

SC reports honoraria and reimbursement for talks on ADHD from the Association of Child and Adolescent Mental Health, British Association of Psychopharmacology, and the Canadian ADHD Resource Alliance and Healthcare Convention. PA reports honoraria for consultancy to Shire/Takeda, Eli Lilly, and Novartis; educational and research awards from Shire, Lilly, Novartis, Vifor Pharma, GW Pharma, and QbTech; and speaking at sponsored events for Shire, Lilly, Flynn Pharma, and Novartis. ES-B reports personal fees from Shire and Neurotech Solutions. TB reports personal fees for being on the advisory board from ADHS digital, Infectopharm, Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Roche, and Takeda. He received conference support or speaker’s fee by Medice and Takeda. He received royalties from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press, outside the submitted work. DB is an unpaid scientific advisor for an EU-funded Neurofeedback trial. JB reports personal fees for lectures from Janssen, Takeda/Shire, and Medice; and personal fees for being on the advisory board from Roche, Medice, Servier, and Angelini, outside the submitted work. DC reports grants and personal fees from Shire and Takeda, and personal fees from Medice, Servier, and Oxford University Press, outside the submitted work. DD reports grants, personal fees, and non-financial support from Shire/Takeda, personal fees and non-financial support from Eli Lilly and
Medice, non-financial support from Qb Tech, book royalties from Hachette, and training and supervision fees from the New Forest Parent Training Programme, outside the submitted work. RWD has received compensation for serving as consultant or speaker, or he or the institution he works for have received research support or royalties from the following organisations or companies: EU (FP7 Programme), US National Institute of Mental Health, German Federal Ministry of Health/Regulatory Agency, German Federal Ministry of Education and Research, German Research Foundation, Volkswagen Foundation, Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier, Shire, Sunovion/Takeda, and Theravance. He was an employee of Eli Lilly in clinical CNS research until August 2008, and owns Eli Lilly stock (small part of the respective annual salary). The drug marketed by Eli Lilly is not mentioned in this guidance. MDo reports grants and personal fees from Eli Lilly, Medice, Shire, Janssen Cilag, Takeda, and Vifor; grants from the German Research Foundation, German Ministry of Health, and Innovation Fund; personal fees from the National Association of Statutory Health Insurance Physicians in Germany, Beltz Publisher, Elsevier, Guilford, Hogrefe, Springer, Wiley, Kohlhammer, and Schattauer. MF reports fees for lectures from Medice and ROVI. CH was an expert member of the National Institute for Health and Care Excellence Guideline (NG87): Attention deficit hyperactivity disorder: diagnosis and management, published in 2018. MH reports personal fees from Medice, Shire, Takeda, Neuroconn, and Hogrefe, outside the submitted work. EK is CSO and Board Member of NLS Pharmaceutics, investigating drugs that are not mentioned in the current guidance. PS reports speaker’s fees paid to his department; and is the CEO and shareholder of HealthTracker Ltd, which is unrelated to the submitted work. CS reports non-personal research funds from Lundbeck and Shire paid to his institution; is a
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Availability of data and material

This guidance represents a synthesis of previously collected data. There are no previously unpublished data included.

Code availability

Not applicable.

Authors’ contribution

All authors played an active role in the conceptualisation, writing of different sections and revision of the manuscript. DC and ES made overall editorial decisions.
Keywords: attention deficit hyperactivity disorder, intervention, evidence-based medicine, guideline
Abstract

ADHD is the most common neurodevelopmental disorder presenting to child and adolescent mental health, paediatric and primary care services. Timely and effective interventions to address core ADHD symptoms and co-occurring problems is a high priority for healthcare and society more widely. While much research has reported on the benefits and adverse effects of different interventions for ADHD, these individual research reports and the reviews, meta-analyses and guidelines summarizing their findings are sometimes inconsistent and difficult to interpret. We have summarised the current evidence and identified several methodological issues and gaps in the current evidence that we believe are important for clinicians to consider when evaluating the evidence and making treatment decisions. These include, understanding potential impact of bias such as inadequate blinding and selection bias on study outcomes; the relative lack of high-quality data comparing different treatments and assessing long term effectiveness, adverse effects and safety for both pharmacological and non-pharmacological treatments; and the problems associated with observational studies, including those based on large national registries and comparing treatments with each other. We highlight key similarities across current international clinical guidelines and discuss the reasons for divergence where these occur. We discuss the integration of these different perspective into a framework for person/family-centred evidence-based practice approach to care that aims to achieve optimal outcomes that prioritise individual strengths and impairments, as well as the personal treatment targets of children and their families. Finally, we consider how access to care for this common and impairing disorder can be improved in different healthcare systems.

Introduction
Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder defined by persistent, impairing and developmentally inappropriate inattentive/disorganized and/or hyperactive/impulsive behaviours that lie at the far end of a normally distributed continuum. (1) ADHD is common, with a worldwide pooled prevalence of around 5.3% in children and adolescents (2) and 2.8% in adults (3). Although epidemiological data suggest that, when the same diagnostic criteria and procedures are applied, epidemiological prevalence rates of ADHD are similar throughout the world, the administrative prevalence for ADHD (rate of clinical diagnosis) varies considerably both between and within countries (4).

ADHD results in considerable burden at an individual, family and societal level and has an important impact on quality of life and daily functioning (5, 6). Patients with ADHD are at increased risk for serious negative outcomes including poor educational outcomes (7), injuries and accidents (8, 9), teenage pregnancies (10), family conflict (11), and criminal behaviour and incarceration (12). ADHD is also commonly associated with other psychiatric and neurodevelopmental disorders (13-20) and a number of physical health conditions (21-23). A recent Australian study (population 24.6 million) (24), estimated the total costs in 2019 as $20.57 billion AUD (£11.3 billion UKP, €12.9M,), which translates to $836 AUD (£459 UKP, €524) per capita. Of this total 63% were attributable to financial costs and 37% to wellbeing costs (those costs associated with reduced quality of life and impaired functioning, and premature death).

While there is now considerable evidence to support the efficacy and safety, at least in the short term, of pharmacological (25) and some non-pharmacological treatments (26) for
ADHD there are also indications that the positive effects seen in clinical trials are not always realized in day-to-day clinical practice (27, 28). The purpose of this paper is to critically discuss the most up-to-date clinical evidence on the potential benefits and harms of the various approaches to the treatment and management of ADHD, to identify the limitations of the current evidence base and the impact of these limitations on interpretation and translation into clinical practice.

This work did not involve primary research and therefore no ethical approval was required. The focus is on children and adolescents because a range of both pharmacological and non-pharmacological interventions has been evaluated in this age range, while the evidence in adults is limited largely to pharmacological interventions. Whilst most clinical trial data have focused on core ADHD symptoms as the primary outcome of interest, an increasing number of studies have recognised the importance of a broader range of outcomes. These include common co-occurring symptoms such as mood lability and those related to coexisting disorders (i.e., ODD, anxiety and depression)(29), functional impairments, quality of life as and more distal outcomes such as criminality (30), traffic accidents (31) and mortality rates (32). We follow this lead on outcome beyond core symptoms in the current paper. As ADHD is usually a chronic and long-term condition (33), we will wherever possible consider evidence that focuses on long-term as well as short-term outcomes.

We will first consider some of the methodological challenges that we encountered when conducting systematic reviews and meta-analyses of ADHD interventions and highlight how these may have affected interpretation of the evidence and discuss some of the approaches that may mitigate these methodological challenges. We then compare different sets of
guidelines in relation to ADHD management, with a particular focus on the common features and highlighting important differences, including possible reasons for these discrepancies. We then discuss how the evidence and guidelines can be translated into high-quality care, and how the clinician can take account of individual symptom profiles, treatment targets and personal circumstances to provide person and family centred approaches to intervention within the current evidence base. Finally, we consider the implications for systems of care and how adherence to evidence-based practice can be implemented across a range of care settings.

The evidence base for interventions

Methodological issues

In this section, summarized in Table 1, we highlight several key methodological issues, consider their potential impact on evidence-based decision making and give some guidance on what aspects to look for when assessing the evidence.

Table 1 about here

Evaluating the quality of evidence - Risk of Bias

Randomized controlled trials (RCTs) remain the gold standard to assess the efficacy, effectiveness and safety of interventions. In the last couple of decades, there has been a greater appreciation of the importance of rigorous trial design and analyses to ensure treatment evaluations are not biased. Standardized instruments, such as the Cochrane Risk of Bias tool (34) and GRADE (35) criteria have been applied to assess potential bias of individual trials and the overall quality of the evidence, respectively. Different review groups
have applied these tools differently and as a consequence come to different conclusions about the overall quality of evidence and how it should be interpreted (e.g. 25, 36). These differences often reflect the way thresholds are set (e.g., number of ‘uncertain’ items required for a study to be rated as ‘high risk’) or different approaches to evaluate the impact of potential conflicts of interest. Unlike considerations for pharmacological interventions, there has, until recently, been little attempt to take account of researchers’ involvement in both the development and evaluation of non-pharmacological interventions as an area of potential risk of bias (but see (37) for a recent advance in the field). In the UK, the National Institute for Healthcare and Excellence (NICE) recently rated the overall quality of evidence as low for non-pharmacological approaches and low to moderate for pharmacological interventions (38). Of note, the evidence level for pharmacological interventions is comparable to the evidence appraisal of some standard interventions for important somatic disorders (e.g., for hypertension (39) and asthma (40)).

Adequacy of blinding: Are patients, clinicians and researchers aware of treatment allocation?

A major potential source of bias and therefore for the quality of RCT evidence relates to the presence and adequacy of blinding – whether patients or assessors of outcomes are aware of who received what intervention. There is potential for un-blinding even during well-designed and carefully conducted pharmacological trials, which it has been suggested could undermine confidence in all of the evidence for efficacy, (e.g. 36). Whilst it is possible that the apparent effects of medication could be exaggerated by un-blinding due to adverse effects, this has not been demonstrated nor has this view been endorsed by the major evidence-based treatment guidelines, (e.g. 41). The potential for bias due to lack of blinding
is particularly acute for psychosocial interventions where: (i) blinding is very difficult to implement with integrity and (ii) patients/parents are often the informants for the primary outcomes. To address this problem, the European ADHD Guidelines Group (EAGG), a working group of the European Network for Hyperkinetic Disorders (EUNETHYDIS) estimated the impact of blinding on results in their series of meta-analyses of non-pharmacological treatments for ADHD (26, 42-45). They compared what they termed the “most proximal” outcome (MPROX - i.e., rated by persons closest to treatment delivery and therefore the most vulnerable to lack of blinding) with the measure judged by the group consensus to be most blinded (PBLIND, i.e., probably blinded). These comparisons provided a range of estimates of treatment efficacy adjusted for degree of blinding. The EAGG meta-analyses found that: (i) MPROX effects were considerably larger (and more significant) than PBLIND effects; (ii) the scale of this MPROX-PBLIND discrepancy varied by treatment type – largest for parent training (where blinding was most challenging to implement) and smaller (though still substantial) for neurofeedback and cognitive training and (iii) the stronger the study design (e.g., sham/placebo controlled designs) the smaller the discrepancy. Even in apparently well-blinded studies (with a sham control) PBLIND gave smaller effects than MPROX. These findings highlight that optimal assessment of treatment efficacy should combine blinding by design and blinding by reporter. It is however important to acknowledge that un-blinded outcome measures may still add value, as they may reflect changes in other aspects of the situation that are clinically relevant but not picked up by the blinded raters who may be evaluating more limited range of behaviours.

What are the selection criteria for the clinical sample?
Patient selection entry criteria also represent a potential source of bias and limit generalisability of findings. Most clinicians are aware of the issues relating to non-inclusion in most RCTs of those more complex comorbid cases that are common within their clinical practice. There are however several other issues that are not so obvious. For example, many recent medication trials have included enriched samples, for example, excluding participants who have previously not responded to or had adverse effects from one of the study drugs. Although these criteria were implemented for ethical reasons, they are likely to introduce bias, usually in favour of the study drug. Non-pharmacological trials also typically recruit less complex and hence easier to treat patients for reasons of convenience and this can affect trial findings (37). In non-pharmacological trials, another challenge is that results may be difficult to interpret because of variation in whether participants are receiving ADHD medication, which could reduce the effect of the tested intervention.

**Have long as well as short-term effects been assessed?**

Whilst there is a wealth of data regarding the short-term efficacy of treatments for ADHD, high-quality data on longer-term outcomes are still lacking and the long-term effectiveness of ADHD interventions, both pharmacological and non-pharmacological, continues to be debated (28, 46, 47). The situation has improved somewhat since the European Medicines Agency (EMA) required companies to include longer term efficacy trials of at least 6 months or with a randomised withdrawal period of at least 6 months as well as long-term safety trials of at least one year, as a part of the data presented for marketing authorization (http://bit.ly/1O2XRPP). Several of these randomized discontinuation trials have now been published although few have exceeded the one year duration required by the regulatory authorities (48-51).
A number of studies, including the Multimodal Treatment of ADHD (MTA) study (27) and observational cohort studies provide information about longer-term efficacy and adverse effects. While hugely valuable in many respects, the non-random nature of the data limits the conclusions about causal effects. These designs often include a lack of blinding and biases in a number of factors influencing who remains on medication (e.g. 52, 53).

**Are adverse effects adequately assessed?**

Adequate measurement of short- and long-term adverse effects is often a concern. Whilst adverse events are routinely measured in drug trials which are required to comply with legal and ethical requirements, this has traditionally been through spontaneous self-report and over relatively short time frames. The EMA guidelines on the clinical investigation of medications for ADHD have also insisted that companies conduct open label safety studies of at least 1 year with prospective follow-up for a longer period of time as a part of the Risk Management Plan (RMP) post-licensing ([http://bit.ly/1O2XRPP](http://bit.ly/1O2XRPP)) and have directed that these studies focus on growth and puberty, cardiovascular safety, as well as psychiatric and neurological adverse effects. However, the lack of a comparison group in these studies (e.g. 54), makes interpretation of their findings much more complicated. Very few non-pharmacological trials make any attempt to measure possible adverse outcomes. The assumption that such interventions are unlikely to have any negative effects is perhaps naive and until recently rarely tested (55) and recent work suggests that this may be an under-appreciated phenomenon(56).

**What can we conclude from observational studies?**
Despite their clear limitations (57), observational studies have certain advantages and can helpfully complement RCTs. They importantly often include real-world outcomes, such as criminal convictions (58, 59), violent re-offending (60), depression (61), suicidality (62, 63), substance misuse (64, 65), psychotic disorders and hallucinations in childhood and adolescence (66), childhood injuries (67-69), emergency visits (70-72), and transport accidents (73), motor vehicle crashes (31) and school performance (74, 75). Further strengths of these studies include their large samples and potential for observation over extended periods. Several studies have adopted innovative designs, such as the use of self-controlled case series, e.g. (71) aimed at decreasing the bias due to the lack of randomization in observational studies, in an attempt to mitigate these limitations. However it is still important to recognize limitations that cannot be addressed by the self-controlled case series design, such as the potential for referral bias, lack of control for time varying confounders (69), and the frequent lack of information on the validity of diagnoses and explanatory variables, when considering the often impressive findings.

**How do we assess whether one treatment is better than another?**

Network meta-analysis (NMA) is a relatively recent development in the field of evidence synthesis that allows comparison among different interventions, in order to provide a ranking of interventions based on, e.g., efficacy and tolerability. Supported by the WHO, Cochrane, GRADE and NICE (76), NMAs have several potential benefits (76), including their ability to take into account a much wider range of evidence and make quantitative comparisons between interventions even when they have not been directly compared in head-to-head studies. However, NMA methodology requires a very rigorous and careful approach to ensure accurate and reliable results. A main consideration is the requirement
for transitivity (i.e., that effect modifiers do not substantially differ across the included trials). This is currently particularly challenging when trying to combine evidence from pharmacological and non-pharmacological interventions into a single network of a NMA (77).

A summary of the current evidence

Multiple systematic reviews and meta-analyses have been published assessing the efficacy and/or tolerability of both pharmacological and non-pharmacological treatments for ADHD and these data have been further scrutinized in the development of evidence-based guidelines.

Medication

Efficacy: The most recent and comprehensive appraisal of pharmacological treatments is the network meta-analysis (NMA) conducted by the EAGG, with stringent inclusion/exclusion criteria (such as excluding enrichment designs and RCTs with add-on treatments) as well as including both published and unpublished data. The main findings on efficacy and tolerability are presented in Table 2. These data support general efficacy and tolerability for a broad range of ADHD medications with methylphenidate in children and adolescents, and amphetamines in adults leading the table based on combined efficacy and tolerability profiles. As described above, a significant limitation in our understanding of pharmacological treatments for ADHD relates to the lack of methodologically sound data on longer-term effectiveness WHICH therefore remains uncertain. It is therefore important that studies with more advanced designs such as long-term randomized discontinuation trials as
well as those using within subject designs through linked registry data and data from
electronic medical records are supported and conducted (78).

Table 2 about here

Tolerability and safety: In relation to adverse events and safety, both individual reviews,
meta-analysis and network meta-analysis demonstrate good short-term tolerability of ADHD
medications once the events equally common in treatment and placebo arms are taken into
account. Common short-term adverse effects are well-described and routine monitoring is
part of standard care as discussed in many clinical guidelines (41, 79). The same challenges
described above for identifying longer-term effectiveness also apply to longer-term adverse
events but are compounded by the potential problems of statistical power when trying to
identify rare but important adverse effects such as completed suicide and severe
cardiovascular events. The most effective way to provide these data are through
observational studies using large registry and research databases that can provide
complementary data to that from clinical trials and meta-analyses. It is therefore essential
that these studies are supported and conducted.

Non-pharmacological interventions

Several high-quality systematic reviews and meta-analyses have also investigated the
evidence for the efficacy and effectiveness, but not acceptability or adverse events, of non-
pharmacological approaches to treating ADHD (Table 3). For behavioural parent training,
blinded ratings do not support an effect on core ADHD symptoms but do show a significant
increase in positive parenting and reduction in both negative parenting and children’s
oppositional behaviours (80). The evidence around neurofeedback is most hotly contested, with different research groups presenting different arguments and rationales about which studies should be included, which protocols were used to deliver neurofeedback and which outcomes should be considered (81-85). Positive effects seen with un-blinded outcomes are not sustained when blinded outcomes (43) or sham controls (86, 87) are included in the analyses. While there are studies showing beneficial effects on inattention (86), we recommend that both standard neurofeedback approaches (43), and the more intensive treatments (86) require further evidence and validation before neurofeedback should be considered as standard clinical interventions for ADHD. Cognitive training, defined as “the process of improving cognitive functioning by means of practice and/or intentional instructions”, showed a medium to large effect on unblinded outcomes (26, 42). These effects remained marginally significant for probably blinded outcomes for ADHD symptoms and significant positive effects on laboratory tests of verbal and visual working memory but, importantly, were not significant for attention and inhibition or academic functions. An overview of systematic reviews of dietary interventions concluded that individual study methods were weak and that different meta-analyses have used very different inclusion and exclusion criteria and that this has resulted in a wide range of estimated effect sizes (88). There is a small but statistically significant effect on probably blinded ratings for supplementation with free fatty acids, whilst the evidence to support either restricted elimination diets or elimination of artificial food colours is less certain.

Table 3 about here

International clinical guidelines: key differences
Clinical guidelines are an important mechanism for increasing evidence-based clinical practice, improving quality of care and resource allocation. Several national guidelines from Europe and North America, compared in Table 4, have published recommendations for the management of ADHD in children and adolescents. These come from distinct cultures with very different healthcare systems, and with varying rates of diagnostic identification, and differing availability of both pharmacological and non-pharmacological interventions. Guidelines also vary in the clinical issues addressed and methods for reviewing evidence. Methodological differences include: the use or not of professional reviewers versus clinical experts; the prioritization of expert opinion versus evidence base; undertaking of an independent primary review of the literature or reliance on existing reviews and whether costs of intervention are considered when making recommendations.

The recommendations of the cited guidelines (apart from the Canadian CADDRA guidelines which did not include a systematic review of the evidence) were developed by combining evidence summaries (based on systematic reviews, meta-analyses and assessment of quality of evidence, with the most recent guidelines using the GRADE system for evaluating quality of evidence (35)), with expert opinion.

Despite being largely reliant on the same evidence base, differences in recommendations are especially likely when high level evidence (i.e., meta-analyses randomised controlled trials; RCTs) is lacking. In such circumstance different groups have taken different approaches - the UK NICE (89) and the German Guidelines (90) use expert opinion, the Dutch Guidelines (91) take individual studies into account and the Spanish Guidelines (92) consider the recommendations of other guidelines including NICE and the American
Academy of Pediatrics (93), evaluated using the Appraisal of Guidelines for Research & Evaluation (AGREE) methodology (94). Only NICE and the Dutch Guidelines included health economic evidence when considering their recommendations.

Table 4 about here

### Similarities across guidelines

In summary, in relation to **assessment and diagnosis**

- All guidance specifies who can diagnose and prescribe; European (UK, German, Dutch and Spanish) guidance make specific reference to specialist ADHD training amongst paediatricians and psychiatrists while North American guidance includes primary care physicians. For prescribing, UK NICE guidance also allows shared care plans between specialists and primary care physicians.

- All guidelines agree that the clinical interview and direct observations, including assessments of impairment, physical and psychiatric comorbidity and family history, provide the basis to establish a diagnosis.

- Rating scales are recommended as auxiliary diagnostic tools and as systematic outcome measures in treatment monitoring, rather than as the gold standard for the diagnosis.

- Neuropsychological assessment is not considered to be essential to establish the diagnosis, even though it can provide useful information to better tailor the management.

- In relation to **treatment**:

- All guidelines take account of developmental differences, but some specifically stratify treatment recommendations according to age, with three groups identified:
Young children: under 5 years (NICE) or under 6 years (German and Spanish Guidelines); School-aged children: 5/6-18 years; and adults: >18 years. The Dutch guidelines further differentiated between children 6-12 and adolescents 12-18 years.

- The RCT evidence for efficacy and safety of medication in young children is considered too limited to recommend medication for routine treatment in this age group, but medication is an option that could be considered in selected cases.

- When pharmacological treatment is indicated, most guidelines suggest that stimulants are the preferred first-line medication. The Spanish Guidelines only indicate that any of the approved medications can be used without offering any recommended order of priority.

- All agree on the need for psychosocial interventions but differ in their timing in the management of ADHD. In contrast to the other guidelines, the NICE 2018 Guideline no longer recommends parent training as first-line treatment in school-aged children because of the lower effect sizes and poorer quality of evidence compared to medication, but ADHD-focused parent training remains the first-line intervention for pre-school children.

Guidelines differ in whether they consider ADHD severity as a factor when making recommendations. NICE (2018) currently do not while the German and Dutch Guidelines, adopting the DSM-5 definitions of severity, do. Both the Dutch and NICE guidelines also take co-occurring ODD/CD into account. As the main aim of the severity specifier is to avoid overuse of medication in less severe cases, these different approaches may reflect variation in administrative diagnostic rates, which, for example, are higher in Germany (3.2-6.1%)(95-97) than in the UK (0.5-1.5%) (98). In the Spanish Guidelines, where children are severely
affected, clinicians may prescribe outside the formulary (i.e., use medication in children <6 years old).

Apart from the consensus-based CADDRA guidelines (99) these guidelines include few specific recommendations on personalized approaches to ADHD interventions, including co-occurring conditions, and where these occur, they rely largely on expert opinion, rather than trial evidence.

Table 5 about here

With respect to pre-medication investigations (Table 5) all guidelines take an individualized approach, based on personal and family history of possible cardiac disease together with essential physical assessments including height, weight, blood pressure and pulse. None of the guidelines require routine cardiac investigations, such as an electrocardiogram. For all guidelines, ongoing monitoring includes height, weight, pulse and blood pressures, as well as a systematic review of benefits and possible adverse effects. Guidance varies in the extent it specifies the enquiry around class-specific possible adverse effects.

Translating the evidence and guidance into day-to-day management of ADHD

Careful and close application of evidence-based protocols, such as those employed in the MTA trial, often lead to better outcomes for patients in terms of ADHD symptoms (100) and there is emerging evidence that these improvements can be translated into routine practice (101). Whilst the use of evidence-based guidelines to inform the delivery of treatment is strongly recommended, guidelines usually focus on applying evidence from RCTs at the group level in a probabilistic way to inform decision-making for individual cases. Whilst this is a core principle of evidence-based practice there are clearly other factors that need to be considered alongside the evidence and guideline recommendation. These more general
‘management’ issues are often less well researched and not always as well covered by published guidelines. Whilst it is tempting to rely solely on effect sizes when comparing the possible value of different treatment approaches for a particular patient, it is also important to take account of the methodological limitations described above when considering comparisons between different treatments. It is also important to consider that: 1) different treatment approaches have different mechanisms of action and that these can impact on factors such as duration of action or acceptability and 2) different treatments also target different areas of impairment. The contrasts between different approaches are important to consider both when deciding between pharmacological and non-pharmacological approaches and also within each approach, selecting the interventions most suitable for individual patients. Whilst all of the licensed ADHD drugs primarily target a reduction in ADHD symptoms, impact on other symptoms such as emotional dysregulation and mind wandering as well as indirect effects on associated mood, (102) conduct problems (103) and other functional domains (104) have been demonstrated.

In terms of duration of action, while the non-stimulants atomoxetine and guanfacine have lower effect sizes on ADHD core symptom reduction (105), they have a longer duration of action than stimulants, which may be particularly relevant for some patients (such as those with long day schedules). Parent training, on the other hand, is useful in modifying longer term parent-child interactions, such that there is not only a long-term change in parenting style but also in a child’s behaviour; because these are common problems in ADHD, guidelines have retained parent training as a recommended treatment. While still controversial interventions, both neurofeedback and cognitive training also seek to make long-term changes to brain functioning that go beyond symptom control (106).
both is whether the observed changes in laboratory measures of brain activity and cognition translate to improved symptoms and/or functioning in everyday life. The ‘or’ is important in view of several studies that have indicated a dissociation between improvement in cognition or brain function and symptoms (107).

**Patient and parent priorities;** It is important to ensure that patient and parental priorities, preferences and choices are taken into account through the provision of information, followed by a process of shared decision-making (108). Families will have their own concerns and preferences (109), which may be influenced by personal experience, other family members or information from the wider public or accessed through the media, which can often be inaccurate and contradictory (110, 111). It is particularly important to seek ways to include children and young people in decisions about their treatment, and focus on enabling them to take increasing levels of responsibility for selecting, adhering to, and monitoring their care as they develop (108). Young people must be involved in discussions around transition to adult services (112, 113).

Much of the broader management aims for ADHD can be achieved through high quality psychoeducation offered at the beginning of the treatment process and topped up at intervals thereafter (114). Evidence-based psychoeducation should help families and young people become more knowledgeable about ADHD and co-occurring conditions and their management, considering of their individual, familial and cultural health beliefs and constructs, and their concerns, attitudes and beliefs about ADHD. It should empower them as consumers to take active informed responsibility for their treatment plan and enhance therapeutic adherence (115).
After psychoeducation, a shared management plan should be created, prioritising problems and translating them into aims and action plans. Parents and children may have different priorities for treatment targets and these differences should be identified and discussed to build consensus and focus (108).

*Monitoring to optimise outcomes:* Whilst we strongly support treatment optimization and the use of measurement-based care (116), there are few data on ADHD to guide best practice in this respect. Measurement-based care, aimed at reducing symptoms and identifying adverse events, can improve both short- and long-term clinical outcomes and enhance treatment adherence (101). It is however essential that clinicians also focus on broader outcomes when monitoring care, including quality of life (117) as well as patient/family priorities. For those not achieving optimal outcomes from the first treatment/s, alternative approaches should be considered (118). Whilst the sequencing of treatment options (25, 119, 120) has received some attention, few studies have looked at more general management considerations. Stepped care approaches which present different treatment approaches of increasing intensity dependent on response have been discussed for many years but have not yet been well studied. Several well-designed studies examining various stepped care approaches for ADHD are underway, which, when completed, should give new insights into this approach. (121-124).

*Treating ADHD in the presence of co-occurring disorders:* Co-occurring disorders commonly present a complicating factor when managing ADHD (125). In prioritizing and sequencing treatment decisions, consideration should be given to which condition is causing the most
(acute) distress, which has the most effective interventions, and whether treatment of one is needed before intervention for another is likely to be effective (126-128). There is also evidence that for some co-occurring disorders, integrated treatment for both at the same time is the most effective approach (e.g., ADHD and anxiety (129), ADHD and substance use disorder (130)). There can be important interplay between treatments. These are not limited to drug interactions, which always need to be considered, but might also include interactions between pharmacological and psychological treatments such as reduced medication dose following behavioural treatments (119, 131-133).

**Implications for service organization**

*Multi-disciplinary collaboration:* When developing clinical services for children and adolescents with ADHD, a multidisciplinary team is preferable to facilitate comprehensive evaluations including comorbidities, and to provide a wide range of therapeutic options (126, 134). Patients with ADHD often present with multiple impairments and benefit not only from the interventions provided by psychiatrists and psychologists that target core symptoms, but also from the skills of speech and language therapists, nurses, occupational therapists, psychotherapists and family therapists, who focus on associated conditions, on treatment adherence and the challenges of ADHD for the family. Clinicians should also promote interventions and environmental modifications that increase responsibility and social participation more widely. This includes supporting schools to utilize effective management strategies (135-137) and also promoting ways that the community can be more broadly engaged and supported to help those with ADHD achieve better integration and involvement (138). Community-based staff are well placed to support lines of communication with educational and social care agencies.
Strengthening care pathways; Clinicians and commissioners of services need to consider and seek to reduce the many barriers that limit access to ADHD care (139, 140). These include: limited provision of services; inadequate recognition of ADHD as a potential cause of impairment and distress; complex referral pathways and mechanisms for financial reimbursement. A chronic shortage of appropriately trained health professionals within the workforce also reduces access to the full range of appropriate evidence-based interventions (141, 142).

Service Innovation: The dominant model of care is provision in a clinical setting, one-on-one, with highly trained professionals. However, this model can be expensive and limit access (138). Non-clinical services and combined mental/physical health services may be helpful in the management of young people with ADHD, the delivery of interventions, and reaching those families that have difficulty accessing regular clinical services (138, 143-145). Other non-clinical community settings including charities and support groups as well as online resources and (partly) digital interventions can increase capacity and lower costs without sacrificing effectiveness (138, 144). These approaches may be particularly appropriate for interventions such as parent training, CBT, psychoeducation and coaching (145). The Covid-19 pandemic has accelerated the implementation of online, remote assessments and particularly interventions for ADHD. While necessary during recent periods of social restriction, these have potential longer-term utility to increase access for those living at a distance or otherwise finding it difficult to attend in person. It will be important to ensure that other social groups are not excluded by these innovations. School-based interventions
are associated with moderate to large functional improvements in meta-analyses (146), although not in all studies (147).

Conclusions

ADHD is the most common neurodevelopmental disorder in children and adolescents. Although ADHD presents with varying levels of severity, a substantial proportion of affected individuals experience persistent symptoms and substantial impairment from their core ADHD and/or co-occurring symptoms. Therefore, the accurate identification of ADHD and implementation of effective interventions is essential. There is a substantial evidence base, at least in the short term, for a range of pharmacological and, for non-core symptoms, some non-pharmacological treatments, with considerable consensus across different national guidelines emanating from societies that are diverse in terms of their rates of acceptance and identification and their organization of healthcare. However, as in many areas of healthcare, there are significant methodological problems with much of the research underpinning these guidelines and the clinicians should be aware of these and how they may limit interpretation of the evidence. Despite these methodological concerns, clinicians should be confident that ADHD medications are effective, well-tolerated and safe. Parent training provides an important complement, but largely in relation to reducing additional behavioural problems and improving parent-child relationships. High quality evidence for neuromodulation – including neurofeedback and cognitive training – is more limited and as a consequence these should not currently be recommended as first-line interventions for core symptoms.
Management of ADHD extends beyond the implementation of guidelines and should be seen as a partnership with patients and their parents, underpinned by psychoeducation and a shared, agreed-upon management plan that considers individual treatment priorities and preferences. While standard care is delivered in clinical settings through one-to-one patient/clinician relationships, schools and third sector settings have much to contribute to a comprehensive approach. Future research should evaluate the utility of digital methods for monitoring outcomes and delivering psychological interventions (148), but it will also be important to understand what accommodations are most effective at helping patients and their families access and engage with care.

In summary, ADHD is an important disorder to treat and manage over time, in relation to core symptoms, co-occurring problems and improvement of real-world outcomes. Clinicians should be robust in expecting substantial improvement with evidence-based treatment but should undertake this in partnership and with a focus on outcomes that are meaningful for patients.
References:


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ADHD is a common neurodevelopmental disorder

Epidemiological prevalence rates (5.3% in children and adolescents and 2.8% in adults) are similar throughout the world. Where countries report different administrative prevalence rates, these are due to differences in recognition, diagnosis and recording.

ADHD is associated with a wide range of negative impacts, especially when untreated.

These include other psychiatric disorders, medical conditions, poor educational attainments, problematic work records and interpersonal relationships as well as higher rates of criminality and accidental injury.

Interventions for ADHD can be effective, but the evidence is inconsistent and sometimes difficult to interpret.

Despite some criticisms, the overall quality of evidence (rated by NICE) for the shorter-term efficacy and tolerability pharmacological interventions is low to moderate and comparable to the evidence appraisal of some standard interventions for important somatic disorders, while the quality of evidence for non-pharmacological interventions is more limited. For non-pharmacological interventions, NICE rated the evidence as very low to low. Methodological problems include potential bias related to a lack of blinding, greatest for psychosocial interventions but also to adverse effects in medicinal RCTs. Some studies use selected populations and may not be generalizable. Most (but not all) methodological biases are likely to inflate the estimates of efficacy of the target intervention. While network meta-analysis is a powerful tool for comparing different interventions, the methodology requires a very rigorous and careful approach to ensure reliable results or inaccurate conclusions can be reached.

National and international guidelines agree on many aspects of intervention.

Most divide their recommendations according to the age of the child and all consider a role for both medication and psychosocial interventions, especially parent-training.

Clinical management of ADHD needs to personalize the implementation of guidelines.

Individual treatment plans should build on psychoeducation to develop and monitor personalized treatment targets, in discussion with parents and young people.
More children and young people need access to evidence-based care.

Current service organization models and care pathways need to overcome treatment barriers, improve multi-disciplinary collaboration with other sectors, and make advantage of modern technologies.
<table>
<thead>
<tr>
<th>Methodological problem</th>
<th>Impact of this on research</th>
<th>Impact on clinical decision making</th>
<th>Potential Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequacy of blinding</td>
<td>May inflate the apparent effects of active treatments</td>
<td>Reduces confidence in evidence-based recommendations</td>
<td>Potential for two independent raters, one for efficacy and one for side effect?</td>
</tr>
<tr>
<td>Adequacy of blinding</td>
<td>Inflates effects of treatment</td>
<td>If not considered can lead to overconfident treatment recommendations</td>
<td>Researchers should make greater efforts to include blinded ratings in clinical trials of psychosocial interventions with the optimal approach using a combination of blinding by design and blinding by reporter. When reviewing evidence from studies in which a range of outcomes have been used, reviewers should consider adequacy of blinding. Consider adopting the innovative approach developed by the EAGG which compares the most proximal outcome (MPROX - i.e., the outcome provided by the rater closest to treatment delivery and therefore the most vulnerable to this effect of lack of blinding) - with the measure judged to be most blinded (PBLIND).</td>
</tr>
</tbody>
</table>

Trial design
| The use of pre-specified outcomes in statistical analysis plan | A failure to include, and stick to, pre-specified outcomes when analysing the results of a trial can lead to biases in reporting. These biases will usually result in overestimation of treatment effects through ‘cherry picking’ of the most favourable outcomes | Overestimation of treatment effects and overconfidence in clinical decision making | Ensure that all primary and secondary outcomes are pre-specified in a comprehensive statistical analysis plan at trial registration and that this is published/made publicly available well before recruitment is completed. Ensure that the statistical analysis plan is adhered to and that when reporting results any deviations from the plan or additional are clearly and accurately reported as such in trial reports and publications.

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**Trial selection criteria**

| The use of enriched sample designs, e.g. by excluding participants who have previously not responded to or had adverse effects from one of the study drugs | Although these requirements were introduced for ethical reasons, they are likely to produce biased results, usually in favour of the drug compared to either placebo or an active comparator | Reduces confidence in evidence-based recommendations | Ensure adequate reporting of trial design in reports and inclusion of potential biases in limitation sections. Consider excluding studies with enriched designs from meta-analyses and network meta-analyses

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**Lack of long-term efficacy, effectiveness and safety data for pharmacological treatments**
<table>
<thead>
<tr>
<th>High quality data on long term outcomes is still lacking and the long-term effectiveness of ADHD medications continues to be debated</th>
<th>Limits the strength of recommendations about efficacy and effectiveness of long-term medication use for ADHD</th>
<th>A lack of evidence for long-term efficacy is not the same as evidence for ineffectiveness. Evidence suggests that the use of measurement-based care can lead to long term effectiveness</th>
<th>The use of innovative trial designs including randomised discontinuation trials (REFS) that can evaluate effectiveness over longer time periods. The use of linked registry data and data from electronic medical records to assess longer-term outcomes in real world situations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of accurate data on the potential adverse effects of long-term treatment with ADHD medications</td>
<td>Adverse events are traditionally measured through spontaneous self-report and over relatively short time frames. Recent post-marketing studies for new ADHD medications have extended the time-frame up to 2 years and included structured assessments but have not yet included a comparison group.</td>
<td>Whilst the long term (up to 16 years) data from the MTA study do highlight probably effects of stimulant medications on growth (REF), this, and other recent longer term studies have not identified other serious group level growth and puberty, cardiovascular, psychiatric or neurological adverse effects.</td>
<td>The use of innovative study designs such as... using large cohorts, linked registry data and data from electronic medical records that include well matched comparison groups of unmedicated ADHD participants as well as health individuals.</td>
</tr>
</tbody>
</table>

**Lack of data on potential adverse effects associated with non-pharmacological ADHD treatments**

| Very few trials of non-pharmacological treatments | The assumption that such interventions are unlikely to have any | Clinicians should consider the potential adverse effects that may be associated with non- | Clinical trials of non-pharmacological treatments should routinely include measures of adverse effects |
for ADHD have included measures of adverse effects

negative effects is perhaps naïve and certainly untested.

pharmacological treatments (e.g. potential for parental conflict during parent training; adverse effects from dietary manipulation)

<table>
<thead>
<tr>
<th><strong>Network Meta Analyses</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transitivity assumption</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Include in the NMA only studies that are similar in terms of effect modifiers (demographic/clinical/methodological characteristics)</td>
</tr>
</tbody>
</table>

| **Including pharmacological and non-pharmacological interventions in the same network** | Results may be misleading |
| One type of treatment (e.g., pharmacological or non-pharmacological) may erroneously be favoured over the other |
| Test if control conditions have similar effects before lumping them in the same node; check differences between pharmacological and non-pharmacological studies in patient characteristics; assess the association of high risk of bias for lack of masking with the treatment effects; use Component NMAs and/or individual Patient Data (IPD)-NMAs |
Table 2: Evidence for pharmacological treatments of ADHD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Putative mechanism(s)</th>
<th>Evidence for effect on ADHD core symptoms (total) vs placebo&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Evidence for effects on other aspects of functioning vs placebo&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| **Dex-Amphetamine** *(including lisdexamphetamine and mixed amphetamine salts)* | Block of the reuptake of norepinephrine, dopamine  
Release of dopamine from vesicles into synaptic space | Teachers’ ratings  
Clinician’s ratings  
SMD = 1.02 (0.85 to 1.19)  
Parents’ ratings  
SMD = 1.07 (0.79 to 1.36) | Clinical global functioning  
OR = 7.71 (5.52 to 10.77) |
| **Atomoxetine**                                  | Selective inhibition of presynaptic norepinephrine reuptake  
(although note that in prefrontal cortex the norepinephrine transported is responsible for dopamine reuptake) | Teachers’ ratings  
SMD = 0.32 (-0.18 to 0.82)  
Clinician’s ratings  
SMD = 0.56 (0.45 to 0.66)  
Parents’ ratings  
SMD = 0.60 (0.50 to 0.71) | Clinical global functioning  
OR = 2.28 (1.38 to 3.76) |
| **Bupropion**                                    | Inhibition of the reuptake of dopamine, serotonin, and norepinephrine                 | Teachers’ ratings  
SMD = 0.32 (-0.43 to 1.07)  
Clinician’s ratings  
SMD = 0.96 (0.22 to 1.69)  
Parents’ ratings  
SMD = -0.24 (-0.92 to 0.44) | - |
<table>
<thead>
<tr>
<th><strong>Clonidine</strong></th>
<th>Stimulation of the central alpha-2 adrenergic receptors, increasing noradrenergic stimulation (NE)</th>
<th><strong>Teachers’ ratings</strong></th>
<th>-</th>
<th><strong>Clinical global functioning</strong> OR = 2.78 (0.91 to 8.53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Clinician’s ratings</strong> SMD = 0.71 (0.24 to 1.17)</td>
<td>parents’ ratings</td>
<td>-</td>
<td><strong>Parents’ ratings</strong> SMD = 0.23 (-0.45 to 0.90)</td>
</tr>
<tr>
<td><strong>Guanfacine</strong></td>
<td>Stimulation of central alpha (2)-adrenergic receptors (more selective than clonidine) increasing noradrenergic stimulation (NE)</td>
<td>Teachers’ ratings SMD = 0.63 (-0.35 to 1.62)</td>
<td><strong>Clinician’s ratings</strong> SMD = 0.67 (0.50 to 0.85)</td>
<td><strong>Clinical global functioning</strong> OR = 3.63 (2.36; 5.57)</td>
</tr>
<tr>
<td></td>
<td><strong>Clinician’s ratings</strong></td>
<td>parents’ ratings</td>
<td>-</td>
<td><strong>Parents’ ratings</strong> SMD = 0.23 (-0.45 to 0.90)</td>
</tr>
<tr>
<td><strong>Methylphenidate</strong></td>
<td>Block of dopamine and norepinephrine reuptake</td>
<td>Teachers’ ratings SMD = 0.82 (0.48 to 1.16)</td>
<td><strong>Clinician’s ratings</strong> SMD = 0.78 (0.62 to 0.93)</td>
<td><strong>Clinical global functioning</strong> OR = 5.57 (3.99 to 7.79)</td>
</tr>
<tr>
<td></td>
<td><strong>Parents’ ratings</strong> SMD = 0.84 (0.72 to 0.95)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Modafinil</strong></td>
<td>Mechanism unclear but thought to stimulate central histamine, norepinephrine, serotonin, dopamine, and orexin systems</td>
<td>Teachers’ ratings SMD = 0.76 (0.37 to 1.15)</td>
<td><strong>Clinician’s ratings</strong> SMD = 0.62 (0.41 to 0.84)</td>
<td><strong>Clinical global functioning</strong> OR = 3.22 (1.91 to 5.43)</td>
</tr>
<tr>
<td></td>
<td><strong>Clinician’s ratings</strong></td>
<td>parents’ ratings</td>
<td>-</td>
<td><strong>Parents’ ratings</strong> SMD = 0.46 (0.31 to 0.61)</td>
</tr>
</tbody>
</table>

Data from Cortese et al, Lancet Psychiatry, 2018.
^SMD: standard mean difference, given with 95% confidence intervals

^OR: odds ratio, given with 95% confidence intervals
Table 3: Evidence for non-pharmacological treatments for ADHD

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Putative mechanism(s)</th>
<th>Evidence for effect on putative mechanism(s)</th>
<th>Evidence for effect on ADHD core symptoms (total)</th>
<th>Evidence for other aspects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Behavioural Parent Training</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Behavioural parent training (EAGG)** Daley et al., 2014 | Improve parent child interactions | PBlind  
*Positive parenting*  
SMD = 0.63 (0.47 to 0.78)  
*Negative parenting*  
SMD = 0.43 (0.24 to 0.62) | PBlind  
SMD = 0.02 (-0.30 to 0.34) |                           |
|                                  | Increase positive parenting | Unblinded  
*Positive parenting*  
SMD = 0.68 (0.27 to 1.09)  
*Negative parenting*  
SMD = 0.57 (0.37 to 0.78) | Unblinded  
SMD = 0.35 (0.19 to 0.50) | Unblinded  
*Conduct problems*  
SMD = 0.31 (0.05 to 0.57) |
|                                  | Reduce negative parenting |  |  |                           |
### Parenting interventions for pre-schoolers
Rimestad et al., 2019

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Independent assessor</th>
<th>Parent ratings</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative parenting</td>
<td>SMD = 0.33 (0.13 to 0.53)</td>
<td>Parent ratings</td>
<td>SMD = 0.12 (-0.12 to 0.36)</td>
</tr>
<tr>
<td>Positive parenting</td>
<td>SMD = 0.63 (0.32 to 0.93)</td>
<td>Parent ratings</td>
<td>SMD = 0.51 (0.33 to 0.69)</td>
</tr>
<tr>
<td>Negative parenting</td>
<td>SMD = 0.12 (-0.01 to 0.24)</td>
<td>Parent ratings</td>
<td>SMD = 0.07 (-0.01 to 0.15)</td>
</tr>
<tr>
<td>ADHD symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduct problems</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMD = 0.31 (-0.07 to 0.69)</td>
<td>Parent ratings</td>
<td>SMD = 0.44 (0.17 to 0.70)</td>
<td>Follow-up</td>
</tr>
</tbody>
</table>

### Cognitive Training
Cortese et al., 2015

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Working memory visual</th>
<th>Working memory verbal</th>
<th>Inhibition</th>
<th>Attention</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMD = 0.47 (0.23 to 0.70)</td>
<td>SMD = 0.52 (0.24 to 0.80)</td>
<td>SMD = 0.07 (-0.15 to 0.28)</td>
<td>SMD = 0.14 (-0.19 to 0.48)</td>
<td></td>
</tr>
<tr>
<td>PBlind</td>
<td>SMD = 0.20 (0.01 to 0.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reading</td>
<td>SMD = 0.09 (-0.09 to 0.27)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic</td>
<td>SMD = 0.01 (-0.13 to 0.11)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Organizational skills interventions
Bikic et al., 2017

<table>
<thead>
<tr>
<th>Unblinded</th>
<th>Unblinded teacher reported</th>
<th>Unblinded teacher reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teacher reported organizational skills</td>
<td>g = 0.54 (0.17 to 0.91)</td>
<td>Teacher reported academic performance</td>
</tr>
<tr>
<td>Teacher reported inattention symptoms</td>
<td>g = 0.26 (0.01 to 0.52)</td>
<td></td>
</tr>
<tr>
<td><strong>Cognitive training</strong>&lt;br&gt;Catala-Lopez et al. 2017</td>
<td><strong>Parent reported organizational skills</strong>&lt;br&gt;$g = 0.83 \ (0.32 \ to \ 1.34)$</td>
<td><strong>Parent reported inattention symptoms</strong>&lt;br&gt;$g = 0.56 \ (0.38 \ to \ 0.74)$</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Improve executive dysfunctions supposed to underpin ADHD behavioural symptoms</td>
<td>N/A</td>
<td>Main outcome (treatment response)&lt;br&gt;Clinicians’ ratings&lt;br&gt;OR = 0.33 (0.01-5.64)&lt;br&gt;Parents’ ratings: OR = 0.21 (0.01-3.33)&lt;br&gt;Teachers’ ratings: N/A</td>
</tr>
</tbody>
</table>

**Neurofeedback**

<table>
<thead>
<tr>
<th><strong>Neurofeedback EAGG</strong>&lt;br&gt;Cortese et al. 2016</th>
<th><strong>Attention</strong>&lt;br&gt;SMD = 0.13&lt;br&gt;(-0.09 to 0.36)&lt;br&gt;<em>Inhibition</em>&lt;br&gt;SMD = 0.30&lt;br&gt;(-0.10 to 0.70)</th>
<th><strong>PBlind</strong>&lt;br&gt;SMD = 0.15 (- 0.08 to 0.38)</th>
<th><strong>Unblinded</strong>&lt;br&gt;SMD = 0.35&lt;br&gt;(0.11 to 0.59)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurofeedback</strong></td>
<td>Improve brain dysfunctions supposed to underpin ADHD behavioural symptoms</td>
<td>N/A</td>
<td>Main outcome (treatment response)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------</td>
<td>-----</td>
<td>---------------------------------</td>
</tr>
</tbody>
</table>
| Catala-Lopez et al. 2017 | Improve brain dysfunctions supposed to underpin ADHD behavioural symptoms | N/A | Clinicians’ ratings N/A | Parents’ ratings: OR = 0.49 (0.04-4.65)  
Teachers’ ratings: OR = 0.68 (0.05-5.37) | N/A |
| Bussalb et al. 2017 | Improve brain dysfunctions supposed to underpin ADHD behavioural symptoms | N/A | Clinicians’ ratings, total: N/A | Parents’ ratings: SE 0.32 (p value: 0.013)  
Teachers’ ratings, total: SE -0.11 (p value: 0.37): | N/A |
| Van Doren et al, 2019 | Improve brain dysfunctions supposed to underpin ADHD behavioural symptoms | Parent rating Inattention (studies with non-active controls) | first time point SMD = 0.38; (95% CI 0.14 to 0.61)  
follow-up SMD = 0.57 (95% CI 0.34 to 0.81) | N/A | N/A |
<table>
<thead>
<tr>
<th>Parent rating</th>
<th>Hyperactivity/impulsivity (studies with non-active conditions)</th>
<th>SMD = 0.25; (95% CI 0.05 to 0.45)</th>
<th>SMD = 0.39 (95% CI 0.19 to 0.59)</th>
</tr>
</thead>
</table>

**Dietary Interventions**

<table>
<thead>
<tr>
<th>Restricted elimination diet EAGG Sonuga-Barke et al. 2013</th>
<th>Reduce the undesirable brain effects of specific diet components</th>
<th>N/A</th>
<th>PBlind SMD = 0.51 (-0.02 to 1.04)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N/A</td>
<td>Unblinded SMD: 1.48 (0.35 to 2.61)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Artificial food colour exclusion EAGG Sonuga-Barke et al. 2013</th>
<th>Reduce the undesirable brain effects of artificial food colours</th>
<th>N/A</th>
<th>PBlind SMD = 0.42 (0.13 to 0.70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N/A</td>
<td>Unblinded SMD = 0.32 (0.06 to 0.58)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supplementation with free fatty acids</th>
<th>Produce desirable changes in the</th>
<th>N/A</th>
<th>PBlind SMD = 0.16 (0.01 to 0.31)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N/A</td>
<td>Unblinded SMD = 0.21</td>
</tr>
</tbody>
</table>
| **EAGG**  
Sonuga-Barke et al. 2013 | brain biochemistry | (0.05 to 0.36) |  
|--------------------------|-------------------|----------------|  
| **Polyunsaturated fatty acids (or PUFAs)**  
Catala-Lopez et al. 2017 | Changes brain chemistry in regions supposed to be involved in ADHD | N/A | Across raters:  
OR: 2.14 (0.83–5.57) | N/A |  
| **Amino acids**  
Catala-Lopez et al. 2017 | Changes brain chemistry in regions supposed to be involved in ADHD | N/A | Across raters:  
OR = 1.19 (0.25–5.71) | N/A |  
| **Minerals**  
Catala-Lopez et al. 2017 | Changes brain chemistry in regions supposed to be involved in ADHD | N/A | Across raters:  
OR = 2.93 (0.90–10.15) | N/A |  
| **Herbal therapy**  
Catala-Lopez et al. 2017 | Changes brain chemistry in regions supposed to be involved in ADHD | N/A | Across raters:  
OR = 0.59 (0.17–1.99) | N/A |
Table 4: Current national guidelines for ADHD

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Who can diagnose and prescribe</td>
<td>Diagnosis by specialist psychiatrist, paediatrician or other appropriately qualified healthcare professional with training and expertise in ADHD diagnosis, working in multi-disciplinary ADHD services. Prescribing can be shared with primary care physician. There should be formal shared care arrangements.</td>
<td>Diagnosis by child and adolescent psychiatrist, child psychologist, paediatrician or other appropriately qualified healthcare professional with training and expertise in ADHD diagnosis. Prescribing should be by child and adolescent psychiatrist or paediatrician.</td>
<td>Diagnosis by a trained and qualified healthcare professional; this is in general a psychiatrist or psychologist, or paediatrician, and in some instances a general practitioner, all with appropriate training in diagnosing ADHD and related conditions. Prescribing can in principle be done by every physician but in practice should be done only by physicians with appropriate training and clinical experience, thus psychiatrists or paediatricians; general practitioners are not expected to initiate prescriptions but can continue prescriptions initiated by experts, and if needed, seek advice from experts. The same applies to nurse practitioners who can continue prescriptions initiated by experts.</td>
<td>Professional with specific training to assess comorbidities and Differential diagnosis. Paediatrician, Psychologist, Child &amp; Adolescent Psychiatrist (CAP) or General Psychiatrist for adults) and Paediatric Neurologist can diagnose. Prescribing limited to family doctor, primary care physician, paediatrician or psychiatrist.</td>
<td>Fully licensed and adequately trained clinicians</td>
<td>These guidelines are addressed to paediatricians or other primary care clinicians (PCCs) and state that PCCs may benefit from additional consultative support and guidance from child and adolescent psychiatrists, clinical child psychologists, developmental/behavioural paediatricians, neurodevelopmental disability physicians, child neurologists, or child- or school-based evaluation teams. These guidelines provide recommendations on the prescription for PCCs</td>
</tr>
<tr>
<td>Domains and interventions</td>
<td>Assessment¹ &amp; Diagnosis/Recognition</td>
<td>Assessment &amp; Diagnosis</td>
<td>Screening/prevention</td>
<td>Focus on Interventions:</td>
<td>Assessment &amp; Diagnosis</td>
<td>Assessment &amp; Diagnosis</td>
</tr>
</tbody>
</table>

¹ Assessment includes both diagnosis and recognition.
| Included in guidelines | Management | Information & support | Psychosocial interventions (parent, patient, school-based) | Medication | Neurofeedback | Dietary interventions | Inpatient treatment, rehabilitation & youth welfare services | Transition | Self-help | Assessment/diagnosis/monitoring | Treatment | Participation/re-integration | Patient perspective | Organisation of care | Psychosocial interventions | Pharmacological interventions | Organizational and life skills support and training | Medication | Neurofeedback | Dietary interventions | Psychosocial interventions | Medication and monitoring | Interventions in educational settings | Organisation of care | Implementation |
|------------------------|------------|-----------------------|----------------------------------------------------------|------------|--------------|----------------------|-----------------------------------------------|-----------|-----------|---------------------------------|-----------|--------------------------|------------------------|--------------------------|-------------------------|---------------------------|--------------------------|---------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| Independent systematic review of evidence (yes/no) | Yes | Yes | Yes (based on 2018 NICE REF search but reorganized/re-done and updated with individual studies when evidence was lacking) | Yes (Also considered other Guidelines: NICE REF, American Academy of Paediatrics REF) | Partly for treatment section (=based on published evidence & expert consensus when lack of evidence) | Yes (but the search, which was conducted by the US Agency for Healthcare Research and Quality (AHRQ) was limited to research published before 2016) |
| How evidence evaluated | Systematic review/ meta-analysis, Grade | Systematic review/ AWMF/Grade | Systematic review/meta-analysis, Grade | Evidence level and degree of recommendation SIGN REF | Other guidelines' recommendations scored using AGREE (Appraisal of Guidelines Research and Evaluation) | Systematic review with evidence graded using AAP policies |
| Recommendations based on ADHD severity (Y/N) | No | Yes | Y | Y | No | No |
| Recommendations vary according to age (Y/N) | Yes | Yes | Yes | Yes | Yes | Yes |
| First line treatment recommendation (med or non-med) | Children < 5 years: ADHD-focused group parent training. Medication treatment not recommended | School aged children: 1st ADHD specific information & support. | Medication for moderate to severe ADHD (age 6-18 years); in severe cases for children aged 4-6 after psychological treatment | Children <6 years: 1st Parent/teacher training; medication only considered in case of non-response [NR] to parent/teacher training | 6-12 years: | Children <5 years: Medication not recommended | School-aged children and adolescents: 1st Psychological of pedagogical | Psychosocial interventions for pre-schoolers | For preschool children (4-6 years): Parent and/or teacher-administered behaviour therapy as the first line of treatment |
| Universal recommendation for Psychological intervention (Y/N) and qualifications – for what, how delivered, e.g., group/individual, timing, etc. | Yes | School-aged children and adolescents: ADHD specific information & support with review prior to considering medication | Yes | Psychoeducation; Group based or individual, parent and/or teacher and/or patient based psychological treatment | Yes | Psychoeducation & advice to parents/teachers Preference parent leading for individual or group-based intervention Supervision, training and evidence-based program recommended | Yes | Organizational skills training, Psychoeducation, School/Health Care System/Family coordination, Social skills, Executive function training, Cognitive-Behavioural Therapy | Delivery format not specified | Yes | Psychoeducation to child and family. Delivery format not specified. Educational interventions and individualized instructional supports are considered a necessary part of the treatment plan. |
|---|---|---|---|---|---|---|---|---|---|---|
| Sequencing of medication | Yes | School-aged children and adolescents: 1st methylphenidate, | Yes | 1st stimulants 2nd atomoxetine or guanfacine | Yes | 1st methylphenidate 2nd dexamphetamine | No | Medications recommended (no order specified): methylphenidate, | Yes | 1st long-acting stimulants 2nd Atomoxetine, Guanfacine XR and |
| | | | | | | | | | | Yes (implicitly) “the evidence is particularly strong for stimulant medications and |

**2nd if persistent & significant impairment in at least one domain of life: offer medication**

- If comorbid oppositional defiant disorder or conduct disorder: add in a parent training programme

- For adolescents: 1st Medication

- 2nd If symptoms still impairing in at least one domain of life after medication treatment: offer cognitive behavioural therapy

- Psychological treatment for children younger than 6 years old and for children and adolescents aged 6 to 18 years with mild to moderate ADHD

- Those with behavioural problems + mild-moderate ADHD

- 1st parent-teacher training

- Severe ADHD

- 1st shared decision-making medication or parent/teacher training; In case of NR the other option

- Those without behavioural problems + mild ADHD:

- 1st parent-teacher training

- Moderate-severe ADHD:

- Shared decision-making medication or parent/teacher training; In case of NR other treatment option

- 13-18 years:

  - Without/with behavioural problems + ADHD mild: 1st CBT with adolescent and parent/teacher involvement + ADHD moderate-severe: shared decision-making CBT with adolescent and parent/teacher involvement or medication; in case of NR other treatment option

- 1st shared decision-making medication or parent/teacher training; In case of NR other treatment option

- 2nd Medication only recommended if 1st does not work, or in severe cases.

- Adults: 1st pharmacological treatment in moderate to severe cases. Optional to use psychosocial OR medication in mild cases

- For children 6–11 years of age: FDA-approved medications for ADHD and/or evidence-based parent- and/or teacher administered behaviour therapy as treatment for ADHD (preferably both)

- For adolescents 12–18 years of age: FDA-approved medications for ADHD with the assent. Evidence based training interventions and/or behavioural interventions as treatment of ADHD, if available.
<table>
<thead>
<tr>
<th>Health economics included</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>No</th>
<th>No</th>
<th>No</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient/caregiver opinion included in Guideline</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Balance between evidence- and Opinion-led:

1= exclusively or almost exclusively evidence based
2= mainly evidence based but expert opinion where absence of evidence
3= mainly expert opinion

Footnotes

1 2008 NICE Guideline only REF
2 2016 NICE Guideline Addendum REF
Table 5

Guideline recommendations on investigations prior to initiating medication and ongoing monitoring during treatment

|----------------------------------------------------------------|--------------------------------------------------|----------------------------------|----------------------------------|-----------------------------------|--------------------------------------------------|--------------------------------------------------|
| **Pre-medication checks**                                      | • Medical history relevant to possible drug contraindications  
• Height, weight, pulse, blood pressure  
• Cardiology referral or ECG only under specified circumstances (history or clinical signs of cardiac disease; family history of cardiac disorder)  | • Medical history relevant to possible drug contraindications  
• Height, weight, pulse, blood pressure  
• Cardiology referral or ECG only under specified circumstances (history or clinical signs of cardiac disease; family history of cardiac disorder)  | • Medical history relevant to possible drug contraindications  
• Height, weight, pulse, blood pressure  
• Cardiology referral or ECG only under specified circumstances (history or clinical signs of cardiac disease; family history of cardiac disorder)  | • Height, weight blood pressure and pulse  
• Medical evaluation to rule out medical causes of inattention, hyperactivity and impulsivity  | • Weight, height, blood pressure, heart rate, history of light headedness, shortness of breath, or other possible cardiac symptoms, and any family history of suspected cardiac sudden death  | • Child or adolescent’s history of specific cardiac symptoms in addition to the family history of sudden death, cardiovascular symptoms, Wolff-Parkinson-White syndrome, hypertrophic cardiomyopathy, and long QT syndrome. |
| **Ongoing monitoring for all medication classes**              | • Systematic review of systems  
• Assess symptom change  
• Height, weight, pulse and blood pressure  | • Systematic review of systems  
• Assess symptom change  
• Height and weight, pulse and blood pressure  | • Systematic review of systems  
• Assess symptom change  
• Height and weight  
• Pulse and blood pressure  | • Weight, height, Blood pressure and pulse monitoring is recommended to assess possible cardiovascular & growth effects of medication  | • Height and weight in children  
• New mood, anxiety, substance use disorder, psychotic or manic symptoms  
• Suicidal behaviour or ideation  
• Aggressive behaviour (new or worsening)  
• Sleep, appetite  
• Irritability / mood swings  | • Height, cardiovascular parameters (mentioned, not specific recommendation) |
<p>| <strong>Class-specific Ongoing monitoring</strong>                          |                                                  |                                  |                                  |                                   |                                                 |                                                 |</p>
<table>
<thead>
<tr>
<th>Medication</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants</td>
<td>- Tics, Potential for stimulant diversion&lt;br&gt;- Tics, Potential for stimulant diversion&lt;br&gt;- Tics, Potential for stimulant diversion&lt;br&gt;- Not mentioned</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>- Sexual dysfunction&lt;br&gt;- Sexual dysfunction&lt;br&gt;- Not mentioned</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>- Sedation, somnolence, fatigue&lt;br&gt;- Sedation, somnolence, fatigue&lt;br&gt;- Not mentioned</td>
</tr>
</tbody>
</table>