Non-pharmacological interventions for attention-deficit hyperactivity disorder in children and adolescents

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Attention-deficit hyperactivity disorder (ADHD) affects approximately 5% of children and adolescents globally and is associated with negative life outcomes and socioeconomic costs. First-generation ADHD treatments were predominantly pharmacological; however, increased understanding of biological, psychological, and environmental factors contributing to ADHD has expanded non-pharmacological treatment possibilities. This Review provides an updated evaluation of the efficacy and safety of non-pharmacological treatments for paediatric ADHD, discussing the quality and level of evidence for nine intervention categories. Unlike medication, no non-pharmacological treatments showed a consistent strong effect on ADHD symptoms. When considering broad outcomes (eg, impairment, caregiver stress, and behavioural improvement), multicomponent (cognitive) behaviour therapy joined medication as a primary ADHD treatment. With respect to secondary treatments, polyunsaturated fatty acids showed a consistent modest effect on ADHD symptoms when taken for at least 3 months. Additionally, mindfulness and multinutrient supplementation with four or more ingredients showed modest efficacy on non-symptom outcomes. All other non-pharmacological treatments were safe; clinicians might tolerate their use but should educate families of childrenand adolescents with ADHD on the disadvantages, including costs, burden to the service user, absence of proven efficacy relative to other treatments, and delay of proven treatment.

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Introduction

With a global prevalence of approximately 5%, attention-deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterised by inattention, overactivity, and impulsivity.[1] Childhood ADHD predicts the development of future mental disorders and substantial impairments in educational, vocational, financial, and interpersonal and relational domains.[2–5] ADHD reduces life expectancy, increases care duties for families, undermines work productivity, elevates risk for crime, and is costly to the public (annual cost of illness for adult ADHD is more than $8000 per person).[6–9] ADHD increases risk for unemployment and public assistance, with ADHD versus non-ADHD disparities exceeding racial and gender disparities.[10] Therefore, remediation of paediatric ADHD is a promising avenue to prevent negative outcomes in adulthood and socioeconomic costs. It should be noted that symptoms typically recur when treatment discontinues.[11] Therefore, continued research that expands and improves treatment options is necessary.

The heterogeneous contributors of ADHD are a function of biological and environmental factors, so treatments must be individualised and target both mechanisms (figure 1).[12] For example, ADHD is highly heritable, polygenic, and linked to neurotransmitter deficiencies (with emerging research supporting additional biological mechanisms such as inflammation, nutrient deficiencies, infections, and gut dysbiosis).[13–17] However, environmental (eg, parenting style, classroom characteristics, toxins, and nutrition) and psychological (eg, self-management strategies, beliefs, and thinking styles) factors also influence

Key messages

- All non-pharmacological treatments were safe, but none showed a strong and consistent effect on ADHD symptom outcomes when gold standard research designs were evaluated
- On the basis of its effect on participant and caregiver impairment, behaviour, and stress, (cognitive) behaviour therapy can be recommended as a primary paediatric ADHD treatment
- Mindfulness, multinutrient supplementation with four or more ingredients, and polyunsaturated fatty acids can be recommended as secondary paediatric ADHD treatments on the basis of modest efficacy, especially on non-symptom outcomes (eg, impairment and caregiver behaviours)
- There was no effect in well controlled randomised controlled trials on outcomes that are meaningful to participants for cognitive training (digital interventions) and neurofeedback; these are not recommended at our current state of knowledge
- There was inconsistent evidence for the efficacy of some body therapies (eg, acupuncture and massage) requiring stronger research, but some body therapies can be tolerated in the meantime, as they are safe and have general health benefits
- There were insufficient randomised controlled trial data to draw conclusions about the efficacy of dietary interventions, most supplements, brain stimulation, physical activity, and some body therapies (eg, chiropractic), although there are some encouraging pilot data

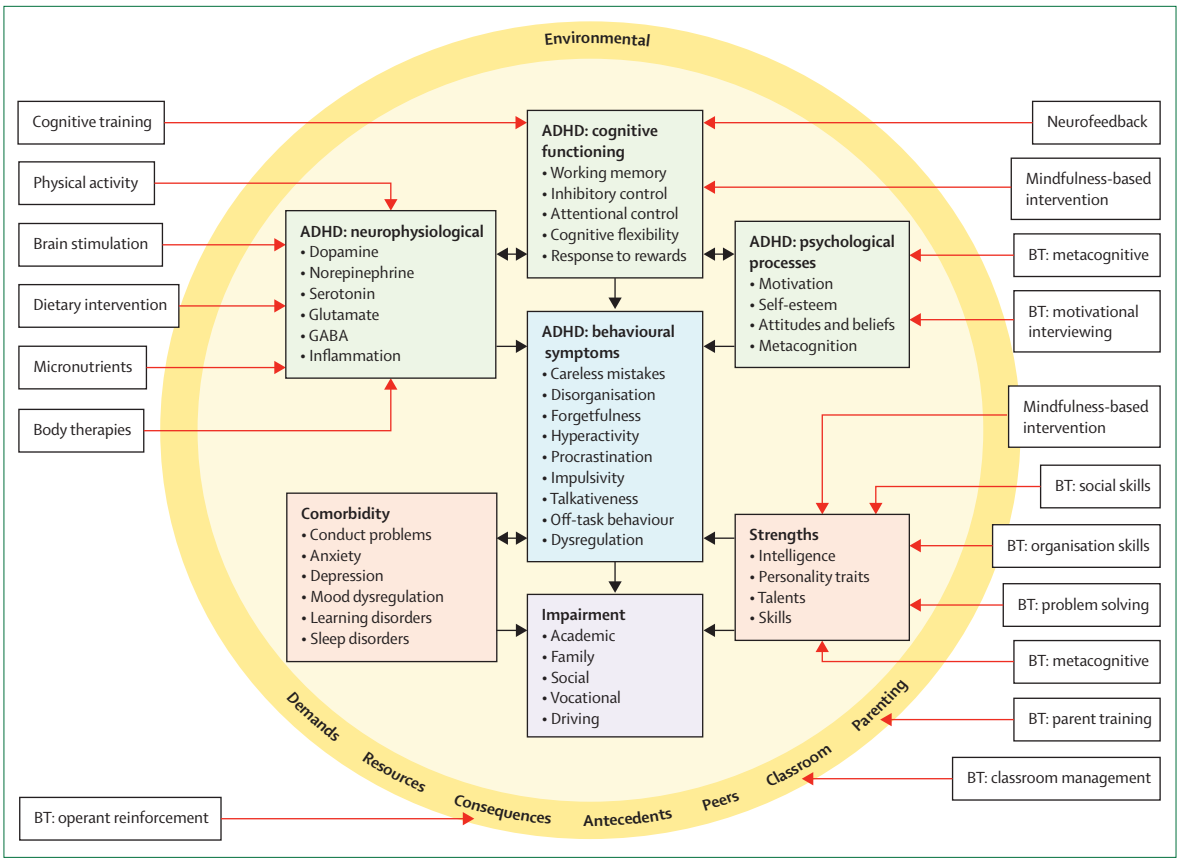

Figure 1: **A theoretical model of factors that influence ADHD severity and the treatments that target them**
ADHD treatments and the mechanisms that they are proposed to target are illustrated. Level of evidence for the effect of treatments on targets are summarised in the appendix (pp 120–237). BT=behaviour therapy. GABA=γ-aminobutyric-acid.

See Online for appendix

ADHD severity, and are reasonable intervention targets.[18–21]

Personalised medicine matches people to treatments based on individual risk profiles (figure 1). Increased recognition of factors contributing to ADHD expands treatment possibilities. First-generation ADHD-treatments were largely pharmacological and targeted biological mechanisms, including methylphendiate, which was initially discovered by accident in an attempt to alleviate paediatric headaches.[22] CNS stimulants, and, more recently, non-stimulants directly remediate neurophysiological dysfunction.[23] However, medications do not target non-biological contributors that exacerbate biological risks. Additionally, some participants and caregivers have negative perceptions toward medications, and some participants cannot tolerate the side-effects or have insufficient benefits from the medications.[24,25] Thus, non-pharmacological treatments have an important potential role in ADHD treatment. However, as availability of these treatments increases, questions arise about which are safe and efficacious, and under what circumstances they should be applied.

Herein, we summarise the extant non-pharmacological treatment literature for paediatric ADHD. We emphasise research using gold standard designs (ie, parallel-group randomised controlled trials [RCTs] and meta-analyses of RCTs) and outcomes that are meaningful to people with ADHD and their families.[26,27] We consider benefits and disadvantages of available treatments and definitions of efficacy, acknowledging that ADHD symptom reduction is only part of the clinical objective.[28,29] Since ADHD is chronic, with symptoms or impairments usually persisting into adulthood, practical symptom management and reduction of impairments that people with ADHD care about is typically the goal.

Methodological considerations

There is often confusion about the value of non-pharmacological ADHD treatments owing to a complex literature with several inevitable and unfortunate methodological complications.[30] First, unlike ingested treatments, many non-ingested treatments cannot be fully blinded (eg, parent training, exercise, and body therapies). Sometimes face-valid shams are developed to promote blinding, but even these can have questionable differentiation from active treatment or invite confounds (eg, parents sharing strategies in sham behaviour therapy and non-specific cognitive training indirectly affecting

Panel 1: Operationally defined categories of non-pharmacological intervention

Behaviour therapy is an intervention directed at modifying behaviours (ie, increasing desired behaviours and decreasing undesired behaviours) based on social learning principles and other cognitive theories. These interventions include classical and operant contingency management, behaviour therapy (mainly through mediators such as parents or teachers) and cognitive behaviour therapy (eg, organisation skills training, problem solving strategies, social skills training, and metacognitive strategies such as cognitive restructuring). These treatments are usually offered in several sessions over time, through training the parents or teachers, the child, or both.

Cognitive training represents a non-pharmacological therapeutic approach that is distinct from more traditional psychological treatment approaches such as cognitive behavioural therapy. Specifically, rather than targeting cognitive components such as maladaptive patterns of thought as in more traditional cognitive therapy, cognitive training is focused on improving, or training, presumed underlying deficits in cognitive abilities such as attentional abilities, working memory, and behavioural inhibition. This training is accomplished through the repeated practice of the use of these abilities with progressively more difficult stimuli and tasks as performance improves.

Neurofeedback integrates principles of neuroscience and instrumental learning (ie, operant conditioning), aiming to augment one's ability to regulate the brain's electrical activity. Electroencephalographic (EEG) electrodes at specific locations on the scalp measure the brain's electrical activity, which is quantified and shown on a screen as feedback, often augmented by auditory rewards or points, to facilitate regulation of specific frequency bands or other electrical activity. In the most widely used neurofeedback protocol, slow wave power (θ band) is targeted for reduction and faster wave power (β band) is targeted for increase. Other cortex-oriented neurofeedback protocols target slow cortical potential or sensorimotor-rhythm. Newer strategies target deeper structures through low-resolution EEG tomography or use functional MRI or near-infrared spectroscopy for the feedback signal.

Body therapies include massage therapy, which involves exerting pressure on a participant's body (often with a therapist's hand); there are different types of massage therapy, such as Swedish massage, Thai massage, tuina, and reflexology. Acupuncture involves inserting thin needles through the skin on a participant's body (including auricular therapy—acupuncture of the ear). Vestibular stimulation involves activation of the vestibular system located within the inner ear, such as through motions (eg, sit and squat in a swivelling chair or jump on a trampoline while rotating the body). Chiropractic therapy involves manual manipulation of the spine and joints.

Vitamins, minerals, fatty acids, and other supplements include single nutrients or multinutrient interventions of four or more ingredients. Vitamins, minerals, fatty acids, and amino acids are all compounds required for normal physiological processes and growth. Since these compounds cannot be synthesised by the human body, many are deemed essential, meaning they must be obtained through diet or supplementation. Herbs, as extracts, are non-essential isolated plant compounds that are thought to have beneficial effects on human physical and mental health and functioning.

Dietary interventions for ADHD treatment involve the modification of one's diet, either by following a healthy dietary pattern (eg, Mediterranean diet), or by the elimination of foods (eg, top allergens such as eggs and dairy), food additives (eg, colours and flavours), and food components (eg, salicylates) associated with a hypersensitive reaction in children. The Mediterranean diet emphasises consumption of fruit, vegetables, nuts, grains, and fish, whereas the elimination diet, also known as the oligoantigenic diet or the few foods diet, restricts consumption of allergenic foods. The Feingold–Kaiser Permanente diet eliminates artificial food colours, additives, and salicylates.

Mindfulness-based intervention is an intervention that teaches mindfulness meditation techniques as the predominant treatment component that targets a clinical outcome. The construct of mindfulness is a complex, multi-faceted phenomenology derived from Buddhism that can be difficult to comprehensively define, although one commonly accepted definition is that mindfulness involves adopting a non-judgmental and accepting attitude with attention towards one's experience in the present moment. In mindfulness-based interventions, meditation is a practice whereby an individual can develop mindfulness. Mindfulness-based interventions are part of the third wave of psychological treatment, which emphasises acceptance and mindfulness strategies. Mindfulness-based interventions are commonly done in group settings. Although initial applications of mindfulness-based interventions were developed for adults, they have also been adapted to train parents and children.

Physical activity is the focus of exercise interventions; this includes physical activity with a self-control component (eg, martial arts) and physical activity based solely on aerobic exercise. Physical activity is proposed to improve ADHD symptoms by enhancing cognitive performance, possibly through reducing inflammation or directly influencing neurotransmission.

Brain stimulation is an intervention influencing brain activities (eg, changing action potential or spontaneous neural network excitability in targeted brain regions) via electric currents. These interventions include transcranial direct current stimulation (mainly through modulating spontaneous neural network excitability), alternating current stimulation, trigeminal nerve

(Panel 1 continues on next page)

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stimulation (using a battery-powered device to stimulate a nerve on the forehead called the trigeminal nerve), transcranial magnetic stimulation (inducing weak electric currents in the brain through rapidly changing magnetic field), and random noise stimulation (ie, the stimulation waveform is a noise signal, using a pair of electrodes to induce weak alternating current oscillating at random frequencies). These treatments are usually offered in several sessions over time, often through non-invasive procedures applied close to targeted brain regions.

targets). Second, sometimes non-pharmacological studies use cognitive tasks as a primary outcome. These analogue paradigms do not correlate with day-to-day functioning, cannot account for temporal or situational symptom variability, and do not usually translate into outcomes that are meaningful to children with ADHD and their families.[31] Thus, we distinguish findings based on gold standard ADHD symptom measures (ie, parent and teacher reports of behaviour over extended periods) from cognitive task performance.

One particularly problematic confounder is that parents and teachers are sometimes involved or invested in non-pharmacological treatment, leading to possible measurement biases. This bias creates a conundrum, because parent and teacher ratings are gold standard measures of outcome in trials of children and adolescents with ADHD; however, these raters also are not fully blinded to treatment. Proposed solutions are suboptimal. Briefly sampled observations of child behaviour might not represent typical behaviour—particularly when a child knows they are being observed. Masked raters of clinical improvement often receive all information from an unblinded source (ie, parents, teachers, or the person with ADHD). Outcome measurement in a setting outside the intervention's scope (eg, teacher ratings measuring response to parent training) sets a stringent criterion for success (ie, generalisation to a secondary setting). We wonder whether these thoughtful attempts at blinding impose greater validity threats than possible pro-treatment biases associated with unblinded but gold standard raters.

Finally, we note an important red herring in this literature—large within-subjects treatment effects in the absence of a control group. ADHD symptoms in untreated control groups typically decline over the course of a study, often by a large effect size.[32,33] This effect might be due to regression to the mean, maturation, placebo effects, or baseline symptom exaggeration by stakeholders trying to ensure study acceptance. Even randomised crossovers can have unavoidable carryover effects for non-pharmacological treatments when therapeutic effects build over time, have delayed onset, or show maintenance (eg, behaviour therapy, cognitive training, and polyunsaturated fatty acids). Because crossovers can be challenging to interpret in these scenarios, when stronger designs were available, we avoided reviewing crossover studies.

Considering these important methodological issues, we avoided studies with design limitations that threatened our conclusions' validity (appendix pp 4–13). We did not rate each study's risk of bias or adequacy of power but instead provide narrative summaries of overall evidence quality[34] and extracted detailed study design data in the appendix (pp 15–16, 27–119). When possible, we review mechanisms of action, long-term efficacy, safety, and cost. We discuss non-blinded studies but comment on the differences between valid blinded and non-blinded ratings when appropriate. We review evidence for non-pharmacological interventions (see definitions in panel 1) as stand-alone treatment and adjunct to other interventions, and draw initial inferences about combinations of non-pharmacological (and pharmacological) ADHD treatments—probably the future of personalised medicine.[28]

Behaviour therapy: recommend as a primary treatment

Behaviour therapy (also called cognitive-behavioural therapy) has a large literature with many high quality RCTs, albeit without full blinding (appendix pp 15–16, 27–43). Behaviour therapy has a complex literature; attempts to summarise it have produced widely divergent conclusions about efficacy.[23,35,36] Importantly, behaviour therapy has very high intervention heterogeneity—treatments are overwhelmingly multicomponent (often with three or more components; figure 2; appendix pp 27–43). Therefore, we could not reasonably organise existing packages into orthogonal subcategories, as others have attempted. Operant reinforcement was present in almost all behaviour therapy packages, as was parent training. Youth skills components are present in about half of all packages and cover heterogeneous topics such as social skills, problem-solving, organisation strategies, and metacognitive skills. A smaller minority of packages include teacher-directed intervention components or motivational interviewing, an engagement strategy with gaining popularity to overcome known barriers to behaviour therapy.[37] We note diversity in treatment intensity, duration, setting, providers, and participant types. Developmentally, youth-directed cognitive components and engagement strategies are almost always integrated into adolescent treatments, whereas childhood behaviour therapy models sometimes solely engage a parent or teacher to deliver operant reinforcement. Although no clear patterns of dose–response or component–response emerged in our analysis of the literature, divergent conclusions about behaviour therapy

efficacy might be a function of intervention heterogeneity and moderating factors. Unfortunately, this variability offers opportunities to cull, organise, and amalgamate findings to confirm reviewer expectations. Providers are often left confused about whether to recommend behaviour therapy.

The issue of blinding is at the forefront of discussions about the efficacy of behaviour therapy.[23,35] It is impossible to fully blind behaviour therapy participants and maintain a well designed study. Thus, nearly all conclusions about behaviour therapy's efficacy hinge on an inference that informant biases cannot possibly be the sole driver of large and robust behaviour therapy effects in scores of well designed RCTs. However, some experts dispute this inference.

Meta-analyses of RCTs find small to medium effects of behaviour therapy on ADHD symptoms, small effects on academic outcomes, small to medium effects on parenting, and medium to large effects on organisation skills (appendix pp 120–43). However, summary statistics mask this literature's heterogeneity, which has important implications for treatment selection. Some behaviour therapy packages are more effective for some people with ADHD than others, and varying treatment doses might be needed to achieve efficacy.[38,39] For example, courses of behaviour therapy packages with evidence of efficacy ranged from 2 h to hundreds of hours—as did courses of therapies without efficacy (appendix pp 27–43, 120–43). Positive response to various behaviour therapies is associated with parental engagement in treatment and family advantages (appendix pp 120–43). However, these moderators might not be relevant for youth-directed treatments. Positive response also is associated with female sex, concomitant medication, older age, ADHD-inattentive presentation, higher anxiety levels, and therapist quality (appendix pp 120–43). However, these moderators are treatment-specific and cannot be generalised to behaviour therapy broadly. Integrative and big data analyses are greatly needed to draw conclusions on which behaviour therapies work for whom and why. Several teams have made advancements in this area, but work is just beginning.[40,41] Although sound treatment matching data is not yet available, modular behaviour therapies might allow clinicians to individualise components to client needs based on clinical judgment. Engagement-focused approaches that integrate parent and youth preferences in treatment are also emerging. These tailored, patient-centred treatments outperform standard behaviour therapies in research trials.[41]

Unlike medication trials, a minority of behaviour therapy RCTs test basic efficacy using gold standard ADHD symptom measures. Instead, most focus on at least one broader, but meaningful, outcome for people with ADHD (eg, impairment, problem-behaviour reduction, or parenting).[26] With respect to ADHD symptoms, about half of behaviour therapy packages show a significant effect in RCTs. However, most studies of behaviour therapy packages find between-group reductions in impairment (eg, academic and social) or broader mechanisms such as youth strategy application (eg, homework skills and organisation), parent or teacher-behavioural changes (eg, positivity and using

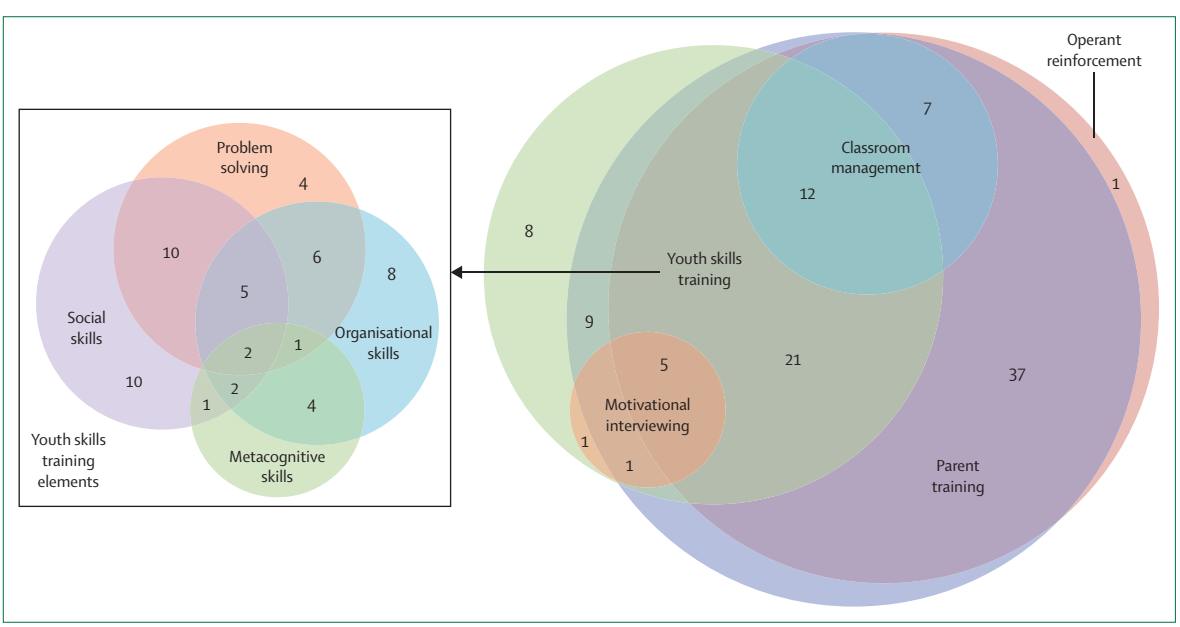

Figure 2: **Venn diagrams representing components of behaviour therapy interventions**
Operant reinforcement was present in almost all behaviour therapy packages (90·2%), as was parent skills training (82·4%). Youth (55·9%) and teacher (18·6%) skills training were less common. Youth skills training included social (30·4%), problem-solving (30·4%), organisation (28·4%), and metacognitive (13·7%) skills. Motivational interviewing, an engagement strategy, was bundled into 6·9% of packages. On average, treatments possessed approximately three components. Numbers indicate the number of intervention packages that have that component.

consequences), and youth psychological variables (eg, self-efficacy and social knowledge). Very few studies examine cognitive task performance as a mechanism—and almost none find an effect of behaviour therapy. These findings support theoretical assumptions that behaviour therapy probably indirectly improves ADHD symptoms and impairments by intervening at youth skills, environmental, and psychological levels (figure 1). In contrast to medication, evidence does not support direct effect of behaviour therapy on neurocognition. Regarding long-term efficacy, almost all studies examining maintenance of therapeutic effects find effects 6–12 months post-treatment (appendix pp 120–43). The Multimodal Treatment Study of ADHD (MTA) found almost no efficacy of childhood-delivered behaviour therapy at 3-year through 16-year follow-up.[11,42,43] However, 3 years post-treatment, one large RCT found sustained efficacy of adolescent-delivered behaviour therapy and moderation by age.[44] Thus, behaviour therapy maintenance might increase with a child's age.

Behaviour therapy is regarded as safe; thus, safety assessments are rarely included in behaviour therapy RCTs. One benefit of behaviour therapy, compared with medication, is that it does not suppress growth and weight.[45] Some individuals claim, anecdotally, that behaviour therapy leads to adverse behavioural events;[46] however the opposite appears to be true (appendix pp 120–43), although more research is needed. There is no evidence for behaviour therapy-related decompensation, and only a handful of studies did not find any therapeutic effects for behaviour therapy (appendix pp 120–43), although publication biases might under-represent null effects.

Bigger questions about behaviour therapy's value relate to opportunity cost (ie, whether to forego pharmacotherapy for behaviour therapy). In studies comparing behaviour therapy with medication, most evidence suggests that medication and behaviour therapy similarly reduce ADHD symptoms. As an exception, the MTA showed short-term advantage of stimulants for ADHD symptoms and impairments (appendix pp 120–43). Thus, if participants show a strong preference for behaviour therapy over medication, it seems reasonable to start with behaviour therapy and add medication as needed—particularly given evidence that beginning with behaviour therapy can enhance combined treatment or allow for lower medication doses.[28,47,48] However, behaviour therapy is more costly and burdensome to administer than medication, particularly in community settings, and it might not be universally available.[49] Medication might be considered first when a child or adolescent with ADHD needs immediate symptom reduction or when no adult (parent or teacher) is well positioned to consistently oversee a behaviour therapy programme. About two-thirds of RCTs examining the effect of adding behaviour therapy to medication found behaviour therapy to incrementally benefit functioning (appendix pp 120–43). Combined treatment produced superior gains in child symptoms (mood, disruptive behaviour, and time management) and parenting, and might minimise opportunity costs while capitalising on behaviour therapy's advantages (combined treatment is more cost effective than behaviour therapy alone).[29] Although there is inconsistent evidence regarding behaviour therapy's effect on ADHD symptoms, it has a consistent and strong effect on a broader range of meaningful outcomes for children and adolescents with ADHD. Therefore, behaviour therapy can be recommended as a primary treatment for paediatric ADHD, but providers should always inform families about its relative disadvantages and benefits compared with medication. Behaviour therapy requires consistent participant or parent effort and might not have a direct effect on ADHD symptoms, but typically evidences long-term maintenance.

Cognitive training: tolerate use but educate on limitations

Cognitive training (ie, digital intervention) is designed to remediate neurocognitive deficits presumed to underlie ADHD. Explosive growth in cognitive training was recently punctuated by EndeavorRx,[50] a prescription cognitive training for ADHD, receiving clearance from the US Food and Drug Administration (FDA) and the Conformité Européenne (CE) mark. Similar to behaviour therapy, cognitive training has a large, robust literature with many RCTs and multiple meta-analyses (appendix pp 44–60). Cognitive training shows high heterogeneity in targeted domains (eg, working memory, sustained attention, and inhibitory control) and dosing features. Cognitive training can be adequately blinded; when considering only blinded trials, meta-analyses suggest no effect of cognitive training on ADHD symptoms (appendix pp 144–51). Meta-analyses permitting unblinded studies report variable cognitive training effects for inattention (range: 0·03–0·64) and no hyperactivity or impulsivity effects. Thus, cognitive training effects appear to result from nonspecific effects rather than cognitive exercises.

Most RCTs of cognitive training, including EndeavorRx, do not show effects on gold standard ADHD symptom measures, and those that do are primarily unblinded or small per-protocol studies that did not withstand replication using stronger designs. Very few studies have shown any effect on impairment. By contrast, about half of cognitive training trials show improvement on cognitive measures—mostly analogue tasks. When using informant ratings of cognition, effects were less consistent—highlighting low correlations between analogue task and daily life performance (appendix pp 144–51).

Overall, when weighing evidence from adequately blinded studies, research indicates no clear effect of cognitive training on meaningful participant outcomes

(appendix pp 144–51). Additional work should clarify why improvements on cognitive tasks do not transfer to ADHD symptoms or daily life performance in adequately blinded trials. There is also little information on the safety of repeated cognitive training administration (eg, screen exposure and vision). Cognitive training might be perceived as highly palatable—particularly when described as a game requiring minimal parental involvement. However, with high costs and low efficacy, we are unable to recommend cognitive training for paediatric ADHD. Providers can tolerate cognitive training but should educate families on its cost and absence of efficacy on meaningful participant outcomes.

Neurofeedback: tolerate use but educate on limitations

Neurofeedback also has a robust literature and a tendency for its RCTs to examine ADHD symptoms as a primary outcome. Similar to behaviour therapy and cognitive training, intervention heterogeneity within neurofeedback is high. Neurofeedback can be adequately blinded using shams. Meta-analyses (permitting unblinded trials) conclude that neurofeedback has short-term efficacy on ADHD symptom ratings (appendix pp 152–64). However, all RCTs comparing neurofeedback with sham universally show no effects—including the large, multisite iCan study.[51] Thus, considering very consistent recent data (2011–21) from sham control RCTs, it becomes clear that previously reported ADHD symptom effects resulted from nonspecific effects rather than brain wave training. Head-to-head comparison of different neurofeedback protocols also does not detect group differences (appendix pp 152–64). In mostly unblinded trials, there are inconsistent effects when comparing neurofeedback with behaviour therapy, cognitive training, medication, and biofeedback. As an adjunctive treatment, findings mirror stand-alone evaluations (only one, unblinded, study finds incremental benefit of neurofeedback to medication). Despite a absence of efficacy, neurofeedback is safe.

One benefit of neurofeedback might be that lower doses of medication are sufficient when combining medication and neurofeedback.[51] However, almost no studies examine effect on impairment, and those that do find nearly no effects. Among six blinded sham comparison RCTs, there is mixed evidence for a direct effect of neurofeedback on cognitive tasks. Considering an absence of specific efficacy, potential costs, and participant burden associated with neurofeedback, this treatment should not be recommended. Because neurofeedback appears to be safe, providers can tolerate its use but should educate participants about its absence of specific efficacy. The same time and effort dedicated to more effective treatments might yield similar results at less expense or better results at the same expense.

Body therapies: tolerate use but educate on limitations

Body therapies are highly heterogeneous, and 11 RCTs have studied a very broad range of interventions, including massage, acupressure, acupuncture, auricular therapy, and vestibular stimulation. Blinding is impossible for some body therapies (eg, massage), but possible for others (eg, auricular therapy) with well designed sham. Meta-analyses are scarce (appendix pp 165–70). Among the seven RCTs examining ADHD symptoms (appendix pp 165–70), results are mixed—specifically for acupuncture and auricular therapy. Functional outcomes are rarely evaluated in this literature and results remain inconclusive (appendix pp 165–70). Most commonly, cognitive task performance is the primary outcome in body therapy RCTs, also with mixed results. There have been some favourable effects for body therapy using categorical recovery classifications (consistent with the Chinese classification of mental disorders[52]). However, given the inconsistent findings, high intervention heterogeneity, and variable blinding, the body therapy literature remains underdeveloped.

Thus, there is insufficient evidence to draw conclusions about body therapies' efficacy; more studies with rigorous designs are needed. Most body therapies can be tolerated with minor or rare side-effects (appendix pp 165–70). There appear to be no RCTs for some body therapies commonly marketed for ADHD (eg, chiropractic therapy). Body therapies can be costly and often require multiple sessions over weeks or months, raising questions of opportunity cost (eg, attending body therapy instead of more efficacious treatments). Some participants and their families might prefer body therapy for cultural reasons—eg, improvement in inner balance of Yin–Yang, the disruption of which is thought to contribute to ADHD within the Chinese Traditional Medicine (appendix p 14) framework. Some body therapies are appealing because they are readily available in communities (eg, massage and acupuncture), can be relaxing to receive, and are marketed for ADHD. Clinicians should educate families of children with ADHD about the relative advantages and disadvantages of body therapies, but also acknowledge when a participant's cultural background might support its use.

Supplementation: recommend as secondary multinutrients with four or more ingredients and polyunsaturated fatty acids; tolerate use but educate about limitations

There is a large number of RCTs examining nutrient or melatonin supplementation, with very high heterogeneity within the broad supplement category. Interventions included single supplements (amino acids, herbs, minerals, vitamin D, polyunsaturated fatty acids, and phosphatidylserine), melatonin, and combinations of nutrients. Therefore, we discuss interventions within

several subcategories (appendix pp 20–26) and note variability even within these (eg, number of ingredients, type, and dose). As ingested treatments, supplements can be successfully blinded; however, not all studies have done so. A robust literature base exists for polyunsaturated fatty acids (PUFAs) with fewer studies for most other single nutrients, multinutrients, and vitamin D. Most supplementation RCTs use small samples—only PUFAs have more than one large RCT (ie, N>100; appendix pp 75–102). Similar to neurofeedback, most supplement studies use a gold standard ADHD outcome; however, across subcategories, there was little consistent evidence for an effect of supplements on ADHD outcomes. When results were inconsistent, they often varied by reporter (eg, clinician, parent, and teacher).

Although not confirmed, potential benefits of supplementation include minimal side-effects, mitigating medication side-effects (eg, sleep disturbance and height suppression), treating underlying nutrient and melatonin deficiencies, and providing mechanistic support (eg, increased cerebral blood flow, cell membrane fluidity, antioxidant or anti-inflammatory properties, cellular support, and microbiome changes). Pre-treatment vitamin and mineral concentrations did not typically moderate response, suggesting that testing concentrations might not be useful. For completeness, our extended discussion of supplement subcategories (appendix pp 20–26) considers results from open-label intervention trials for categories with few or no RCTs. Overall, multinutrients combining four or more ingredients (vitamins plus minerals) and PUFAs were the only supplements with replicated effects on clinically meaningful outcomes, with multinutrients affecting impairment levels and PUFAs affecting ADHD symptoms. Although PUFAs have shown a consistent, small effect on ADHD symptoms, this effect might only emerge when taken for at least 3 months in sufficient doses, typically >1 g. There is also evidence to suggest that PUFAs might lower the optimal stimulant dose. Because the effects of multinutrients combining four or more ingredients (vitamins plus minerals) and PUFAs were more modest than primary treatments (eg, medication and behaviour therapy), we recommend them as secondary treatments (appendix pp 203–06). All other supplements have insufficient or inconsistent evidence of efficacy (appendix pp 171–202). These other supplements can be tolerated, but clinicians should educate families of children with ADHD on possible downsides, including insufficient efficacy, cost, burden of daily pill consumption, possible interaction with medication, and opportunity costs of forgoing primary treatments.

Dietary interventions: tolerate use but educate on limitations

Dietary interventions for ADHD have included elimination of artificial food colours, additives, and salicylates (ie, Feingold–Kaiser Permanente diet); removal of antigenic foods (ie, Elimination–Oligoantigenic diet); and following a healthy dietary pattern (eg, Mediterranean diet). Overall, only a handful of RCTs examined elimination diets or the Dietary Approaches to Stop Hypertension (DASH) protocol (appendix pp 207–10). There are no blinded RCTs of dietary interventions, as face-valid sham diets can be challenging to employ. Nonetheless, elimination diets have shown evidence of improving ADHD symptoms compared with healthy eating advice, and the DASH diet reduces ADHD symptoms compared with a control diet. Dietary interventions for ADHD are safe; however, concerns about inadequate nutrition and participant burden exist for elimination diet interventions.

Overall, the nascent literature on dietary interventions requires more rigorous testing before this category of intervention can be recommended. Consulting uncontrolled and crossover studies (appendix pp 20–26), there are several interventions that might be worthy of further testing. For example, crossover data suggests that elimination of artificial food colours might hold promise but requires examination with more rigorous study designs (appendix pp 207–10). At this time, dietary interventions should not be recommended, but they can be tolerated. Providers can emphasise that there are almost no well designed RCTs on dietary interventions and that participant burden might be high.

Mindfulness-based interventions: recommend as secondary

There is a moderate research base on mindfulness-based interventions with nine RCTs, most of which focus on the reduction of ADHD symptoms or other clinically meaningful outcomes. Intervention heterogeneity is high, particularly due to differences in treatment recipients (ie, only children, only caregivers, or both) and dosing (one to 24 sessions). Similar to behaviour therapy, mindfulness-based interventions cannot be blinded without introducing additional validity threats. Thus, possible informant biases cannot be ruled out. Two meta-analyses of mindfulness-based interventions reported medium effect sizes for inattention and small effect sizes for hyperactivity and impulsivity (appendix pp 211–26). Parent-related improvements were the most consistent positive outcome across mindfulness-based intervention trials (eg, parenting stress, mindfulness, and strategy use) with effects favouring mindfulness-based interventions in nearly all examinations (appendix pp 211–26). Overall, all RCTs of mindfulness-based interventions compared with no treatment show evidence of relative ADHD symptom reduction at post-treatment or 6-month follow-up—although some effects were inconsistent within studies. Compared with behaviour therapy, mindfulness-based interventions do not show superiority for ADHD symptoms but do for child emotion regulation. Similarly, psychoeducation and mindfulness-based interventions show similar effects on ADHD symptoms, but mindfulness-based interventions show superiority

on cognitive tasks. Mindfulness-based interventions have offered a significant incremental effect on ADHD symptoms when combined with non-violent resistance parent training (appendix pp 211–26).

Overall, more evidence is needed to draw conclusions about the effect of mindfulness-based interventions on ADHD outcomes, but this literature is quickly growing and might stabilise soon. Similar to multinutrients with four or more ingredients, there is consistent—although modest—evidence that mindfulness-based interventions affect other clinically meaningful outcomes, particularly parenting stress and behaviour. Future research should examine the safety of mindfulness-based interventions for ADHD (rarely reported).[53] Because mindfulness-based interventions show modest but consistent evidence for broad outcomes such as parental stress, parenting style, and youth emotional functioning, they can be recommended as a secondary treatment for children and adolescents with ADHD (appendix pp 211–26).[54–59] However, practitioners should consider and provide information about the advantages of primary treatments (ie, medication and behaviour therapy) before recommending mindfulness-based interventions, and they should explain the opportunity costs of forgoing primary treatments.

Physical activity: recommend generally, but not as ADHD treatment

Of the 11 RCTs on physical activity for ADHD, most had very small sample sizes and very few considered treatment effect on ADHD symptoms or other clinically meaningful outcomes (appendix pp 111–13). Although there are three meta-analyses reporting small to medium effects of physical activity on ADHD symptoms (appendix pp 227–29), the methodologies of these reports have meaningful limitations. Two of the meta-analyses primarily relied on cognitive tasks as their measure of ADHD symptoms. One generously defined physical activity to include any intervention with movement, thereby including treatments whose primary components are categorised elsewhere (ie, hippotherapy, cognitive training, and behaviour therapy). One challenge in this literature is disentangling immediate cognitive effects of recent exercise from lasting effects of repeated exercise on day-to-day ADHD symptoms. It is also impossible to blind participants (and their parents and teachers) to whether exercise occurred. Thus, additional, better designed trials with a focus on meaningful participant outcomes are needed to confirm the efficacy of physical activity.

Interventions include sports, aerobic activity, and martial arts. Only one RCT examined physical activity's effect on ADHD symptoms and found no effect (appendix pp 227–29). Most RCTs investigate the effect of physical activity on task-based cognitive measures. Results have been mixed and might depend on the amount of time between the exercise session and cognitive task administration. Reducing inflammation is a novel hypothesised mechanism through which exercise might improve ADHD symptoms; one study found mixed results of physical activity on biomarkers of body composition and inflammation (appendix pp 227–29).

Physical activity appears to be inferior to medication for ADHD symptoms. Compared with medication plus behavioural skills class, medication plus physical activity has mixed effects on outcomes. There is also mixed evidence for whether physical activity emphasising self-control (eg, martial arts) is superior to standard physical activity (with cognitive tasks as outcomes). Although there are insufficient scientific data to support physical activity as an ADHD intervention, there are broad health benefits to exercise, minimal financial costs, and possible acute effects on cognition. Therefore, physical activity can be generically recommended to children and adolescents, but not as a primary or secondary ADHD treatment.

Brain stimulation: tolerate use but educate on limitations

Brain stimulation is an emerging treatment for ADHD; similar to the EndeavorRx CT, FDA clearance and the European CE mark have been granted to the Monarch trigeminal nerve stimulation (TNS) device for the treatment of ADHD in children. The literature on brain stimulation for ADHD is very small and highly heterogeneous (appendix pp 114–19). In addition to TNS, the literature on brain stimulation includes RCTs of repetitive transcranial magnetic stimulation (rTMS), transcranial alternating current stimulation (TACS), and transcranial direct current stimulation (tDCS). Duration of tested treatments ranges from one to 30 sessions. Brain stimulation interventions can be adequately blinded using well designed shams.

The evidence in favour of TNS is based on a single small RCT (N=62), in which the Monarch device showed superiority over sham on gold standard measures of ADHD symptoms. This effect is promising but still awaits replication. For tDCs, there was no effect on ADHD symptoms in a trial using sham control. As expected, unblinded trials produce larger effects than blinded, sham trials. For example, unblinded TACS showed superiority to methylphenidate and unblinded rTMS was non-inferior to atomoxetine (appendix pp 230–37). In trials integrating functional impairment measures, no significant between-group differences were detected for brain stimulation versus control, including in the blinded TNS trial. RCTs examining brain stimulation as an adjunct to other treatments find no effects. Mechanisms of brain stimulation are unclear; hypotheses are yet to be confirmed. Results of crossover studies are similar to RCTs (appendix pp 20–26).

Given the few blinded RCTs and, thus far, only unreplicated effects, there is insufficient evidence to recommend brain stimulation to children and adolescents with ADHD at present. Given the heterogeneity of tested

interventions (eg, target brain region, montage, current, and duration), more research is needed within individual intervention types to better understand these treatments and to see if promising initial effects will be replicated. No or minor side-effects are reported; thus, brain stimulation can be tolerated as information about efficacy continues to emerge. However, brain stimulation cannot yet be recommended for paediatric ADHD given its high cost, low availability, and failure to show clear advantages over well established treatments.

Conclusions

Overall, no non-pharmacological treatments showed consistent strong effects on ADHD symptoms. Instead, several non-pharmacological treatments consistently affected broader outcomes that might be equally meaningful to participants, and one treatment (PUFAs) showed a modest effect on ADHD symptoms if consistently taken for at least 3 months.[26] Behaviour therapy is the only non-pharmacological treatment that can be considered as primary paediatric ADHD treatment given its effect on functional outcomes. However, multinutrients combining four or more ingredients, PUFAs, and mindfulness might be considered secondary treatments (effects are consistent, but more modest). All other treatments have either inconsistent or insufficient evidence of effect on participant outcomes (appendix pp 17–19). Although there were several effective non-pharmacological treatments, similar to medication, these interventions remain vastly underused.[60] Therefore, ongoing conversations are needed to educate participants and families about effective, available treatments. Increased use of effective treatments is a top priority for the field.

Integration of non-pharmacological treatments into ADHD care systems will help to maximise engagement in sustained, effective treatment that optimally fits participant values, goals, and presenting problems. Acknowledging the multiple biological and environmental factors contributing to ADHD (figure 1), we recommend combined treatment approaches personalised to the unique factors contributing to someone's symptoms (panel 2). Even when a treatment is not yet recommendable, it might be considered if personalised factors indicate utility (eg, promoting physical activity in a young person with obesity, or promoting Traditional Chinese Medicine for a family valuing the Yin–Yang balance). Treatments without consistent evidence can still be leveraged to facilitate engagement in more effective treatments (eg, motivational interviewing to increase engagement with medication or address patient beliefs that might serve as barriers to behaviour therapy engagement). Similarly, tolerating lower value treatments that are appealing to children with ADHD or their families can build trust that promotes future acceptance of effective treatments.

As evidence for non-pharmacological interventions builds, the health-care sector should develop and evaluate sustainable system-level implementation models that promote the use of evidence-based primary and secondary non-pharmacological treatments, as well as their integration with pharmacological care. For example, there are increasing shifts in non-pharmacological and pharmacological care to lay providers (ie, coaches, technicians, care coordinators, and peers), particularly in the digital era. If care implemented by a lay provider costs less than working with a clinician, this model might increase care availability at the system level. However, it remains unclear if lay providers implement non-pharmacological interventions with sufficient quality and efficacy. For example, recently popularised ADHD coaching is partially redundant with behaviour therapy approaches. Nearly no RCTs examine the safety and efficacy of behaviour therapy implemented by lay coaches; however, a coaching model might promote treatment availability if this workforce proves to be low-cost, receives appropriate training and oversight from clinicians, and is properly regulated. However, some elements of coaching diverge from behaviour therapy (eg, providing ongoing reminders and assistance to youth *vs* supporting autonomy development) and might have adverse effects that require investigation (eg, fostering long-term dependence on the coach) before recommendation of these approaches.

Some treatments are marketed by profit-driven enterprises without adequate disclosure of their product's failure to show meaningful efficacy or yet-to-be replicated results. With widespread direct-to-consumer marketing of these products on social media, clinicians should be prepared to provide clear, accurate information on the advantages and disadvantages of commercially available treatments (appendix pp 17–19) to ensure that participants are shepherded to appropriate care. Primary treatments should be favoured, and opportunity costs considered, before implementing approaches with inconsistent or insufficient evidence.

Since our literature reviews in early 2022, several new papers were published that would probably have met our inclusion criteria;[61,62] however, it does not appear that inclusion of these studies would change the conclusions of this Review. Some important treatment selection factors were outside this Review's scope. Few studies examine developmental differences in care (ie, preschool *vs* childhood *vs* adolescence). Youth involvement in some treatments increases with age, which can threaten engagement but is crucial to supporting the transition to adult care models.[63] Because behaviour therapy is predominantly multicomponent, we could not draw conclusions about efficacy of individual treatment elements. Combined treatment was also underexamined in the literature, as was long-term care. There is almost no research on combinations of effective non-pharmacological treatments (ie, PUFAs, multinutrients,

or mindfulness combined with behaviour therapy), which is an important future direction for research. Sustained non-pharmacological treatment can be a burdensome prospect; however, repeat administrations at key developmental transitions (eg, primary to more advanced schooling) might be a balanced approach to long-term care.

There is a tremendous need for higher quality research on non-pharmacological ADHD treatments. Many studies were excluded from this Review because they used designs with too many validity threats (appendix pp 4–13). Large-scale, well designed, parallel-group RCTs are needed for treatments with insufficient evidence. For large but highly heterogeneous literature bases (eg, behaviour therapy and cognitive training), integrative data analysis techniques can be used to pool datasets to resolve inconsistencies and elucidate treatment moderators, mediators, and dose–response relationships.[40,64] As the research base builds on what ADHD treatments work for whom and why, we will increasingly be able to use personalised medicine approaches to help children, young people, and their families to engage in treatment that works best for them. We look forward to an upcoming generation of research that builds the knowledge base on non-

Panel 2: **Non-pharmacological treatment selection recommendations for children and adolescents with ADHD**

Shared decision making
Even more than with psychopharmacology, shared decision making between the provider and parents is desirable, and children and adolescents should join the treatment selection process when appropriate.

Combined treatment
Emphasise the value of combining multiple primary and secondary treatment approaches (figure 1) in targeting multiple mechanisms that contribute to ADHD symptoms.

Primary treatments
Clearly communicate that pharmacological treatment and multicomponent behaviour therapy are the two established, validated primary treatments for paediatric ADHD. Explain advantages and disadvantages of the two approaches (appendix pp 17–19). Encourage families to try at least one approach while considering the participant's values, treatment goals, presenting problem profiles, and resources.

Secondary treatments
Multinutrients combining 4 or more ingredients, mindfulness, and polyunsaturated fatty acids showed replicated, consistent moderate effects and can be encouraged as secondary treatments in combination with primary treatments or if a primary treatment is not a fit for the participant and their family.

Engagement focused
Assess engagement barriers that might prevent access and sustained participation in treatments that are available locally. When there are strong threats to engagement, consider treatments with the highest likelihood of engaging the participant in any care, even if the treatment plan diverges from ideal practice. Revisit ideal practices once the child or adolescent is adequately engaged in care.

Participant matching
Consider factors that might contribute to an individual child or adolescent's ADHD severity. Systematically assess symptoms and impairment. Match treatment to the mechanisms targeted by available treatments (figure 1). Consider known moderators of treatment for each category. Dose of treatment (eg, duration and intensity) might also need to be tailored to severity of presenting difficulties. Most efficacious treatment programmes include at least 8 weekly sessions attended by the parent and often the child or adolescent with ADHD.

Insufficient or inconsistent evidence: tolerate use but educate on limitations
Treatments with inconsistent evidence might work under some circumstances but not others. Treatments with insufficient evidence might prove to be effective once more research is conducted. Both scenarios reduce the probability of success, but do not eliminate its possibility. All reviewed non-pharmacological treatments with insufficient or inconsistent evidence appear to be safe. Thus, providers should tolerate their use but emphasise the lower likelihood of success for these treatments and opportunity costs of using them instead of primary treatments. Treatments with inconsistent or insufficient evidence of effect on outcomes that are meaningful to participants and their families include:

- Cognitive training (ie, digital interventions)
- Neurofeedback
- Body therapies (eg, massage, acupuncture, and chiropractic interventions)
- Amino acids, melatonin, herbs, single minerals, and vitamins
- Dietary interventions
- Physical activity
- Brain stimulation (eg, trigeminal nerve and transcranial direct current stimulation)

Learn the costs and availability of treatments in your community
Providers should be aware of the availability and costs (financial and time) of local and commercial non-pharmacological treatments for ADHD, as well as the credentials of providers. When a treatment with insufficient or low evidence is offered locally at a high cost (typically by profit-driven entities), providers should be prepared to educate participants about costs of treatment (eg, financial, time, and burden) in relation to its likelihood of success. Low-cost treatments are preferable when evidence is insufficient or inconsistent.

Search strategy and selection criteria

References for this Review were first identified by ten separate searches of PubMed for each category of intervention (see appendix [pp 4–13] for search dates by category). Using the PICO framework (ie, population, intervention, comparator, outcome) we standardised search terms for population:

[(((attention defic*[Title]) OR (attention disorder*[Title]) OR (attention dysfunc*[Title]) OR (hyperactiv*[Title]) OR (hyper-activ*[Title]) OR (hyperkin*[Title]) OR (hyper-kin*[Title]) OR (impulsiv*[Title]) OR (inattentiv*[Title]) OR (inattention*[Title]) OR (minimal brain damage[Title]) OR (minimal brain disorder[Title]) OR (minimal brain dysfunction[Title]) OR (adhd[Title]) OR (addh[Title]) OR (ad/hd[Title]) OR (adhs[Title]) OR (attention deficit disorder with hyperactivity[MeSH Major Topic]) OR (hkd[Title]))] and allowed intervention search terms to vary by category (see appendix [pp 2–3] for search syntax).

Comparator and outcome were allowed to vary across intervention category searches and are reported as findings in this Review. We restricted searches to papers that were published in English; when possible, we incorporated articles in foreign languages (eg, Spanish and Mandarin) according to the language competencies of the research team. After the PubMed search, manual searches were performed by authors based on the reference lists of identified papers. A title and abstract search occurred first, followed by a full text review of papers. Inclusion criteria were: (1) full sample has a diagnosis of ADHD; (2) study evaluated treatment efficacy using quantitative methodology; (3) full sample is paediatric or reports efficacy outcomes for a paediatric subsample (all participants were 19 years or younger).

Within each category of intervention, we examined only randomised controlled trials (RCTs) with appropriate statistical analyses and meta-analyses of RCTs when there were at least three RCTs identified within for specific interventions. Non-randomised observational designs were extracted and reviewed when fewer than three RCTs were identified. We avoided interpretation of within-subject effects in the absence of a control group.

We assigned narrative quality of evidence ratings using an adapted Grading Recommendations Assessment, Development, and Evaluation framework (appendix pp 15–16). Strength of evidence was also rated for each treatment category, adapted from the Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews (appendix pp 17–19).

pharmacological care for ADHD.

Contributors

MHS contributed to conceptualisation, data curation, methodology, project administration, validation, visualisation, and writing the original draft. XZ contributed to conceptualisation, data curation, methodology, visualisation, and writing the original draft. AMB, JMJ, JM, and IH contributed to conceptualisation, data curation, methodology, and writing the original draft. LEA contributed to conceptualisation, methodology, validation, review of the manuscript, and editing. HHB contributed to validation, data curation, and writing of the original draft. PV, LL, FM, ESG, MK, MLJ, CRB, CZ-M, MM, and GT contributed to data curation, validation, review of the manuscript, and editing.

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MHS receives royalties from Guilford Press and has received honoraria from Supernus Pharmaceuticals, and serves as the secretary of the American Professional Society for ADHD and related disorders. JMJ's research received donated products from Hardy Nutritionals and Truehope. JM receives royalties from Guilford Press and consulting fees from Myndlift. JM also receives research funding from the Templeton Foundation and the Duke Center for AIDS research. LEA receives research funding from Roche, Axial, Syneos, Supernus, and Myndlift, and the Foundation for Mental Health. LEA has received consulting fees and support for meeting attendance from Children and Adults with Attention Deficit/Hyperactivity Disorder (CHADD). LEA's research has received an equipment loan from Myndlift and donated products from Hardy Nutritionals. All other authors report no competing interests.

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