Recent advances in the treatment of attention deficit hyperactivity disorder in children: A narrative review

Omkar Dhungel[1], Utkarsh Karki[2], Bikash Sharma[3]

1. Junior Resident, Department of Psychiatry, Patan Academy of Health Sciences, School of Medicine, Lalitpur, Nepal
2. Child and Adolescent Psychiatrist, Child and Adolescent Psychiatry Unit, Kanti Children's Hospital, Kathmandu, Nepal
3. General and Addiction Psychiatrist, Psychiatry Specialties Clinics, Ellicott City, Maryland, USA

Abstract

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by age inappropriate levels of inattention, and or impulsivity and hyperactivity. Often arising in childhood, ADHD can also be chronic in nature, frequently continuing through adolescence and beyond, at least at the level of impairment. The early accurate diagnosis of the condition is possible based on clinic settings, clinicians' expertise; and the context at which screening and evaluation of this population for ADHD is done. ADHD is an etiologically complex neurodevelopmental disorder that begins early in life and has heterogeneous clinical manifestations encompassing a broader spectrum of psychopathology. This underscores the importance of early accurate diagnosis so that effective treatments can be started that significantly reduces immediate and long-term psychosocial burdens. Effective ADHD treatments are available and cognitive neuroscience is rapidly expanding, however there is a significant gap between empirical evidence and clinical practice. Multimodal and multidisciplinary treatment strategies are the best approach in the treatment, but there is a significant gap between the knowledge and practice, such that evidence-based treatments are often not implemented in the community settings. How we implement such in our clinical practice helps us to advocate and advance towards more effective ADHD treatments. There is growing scientific progress in understanding the causes and treatment of ADHD. Knowledge about the evidence-based recent advances in the treatment helps mental health professionals to advocate for the effective approaches to treat ADHD, with minimal unwanted side effects.

KEYWORDS:
ADHD, recent advances, stimulants, neuromodulation, neurofeedback

***Corresponding Author**
Dr. Utkarsh Karki
Child and Adolescent Psychiatrist, Kanti Children's Hospital, Nepal
Email: karkiutkarsh@gmail.com

INTRODUCTION

ADHD is a neurodevelopmental disorder with onset in childhood characterized by symptoms of inattention and impulsivity or hyperactivity that impairs the functioning.Systematic review and meta-analyses have estimated the prevalence of ADHD in children at 5.6-7.6%.[1] It has a clear biological basis as supported by family history, genotyping and neuroimaging studies.[2] Untreated or inadequately treated ADHD has been associated with a broad range of negative outcomes including poor academic performance, difficulties with peer relationships, low self-esteem, high risk taking behavior, parental conflict, psychiatric and medical comorbidity and delinquency.[3] The current clinical guidelines recommend an individualized multimodal and multidisciplinary treatment strategies that includes pharmacotherapy, psychotherapy and neuromodulation. The aim of this review is to discuss the available treatment options and the recent advances in the treatment of ADHD in children.

CONVENTIONAL TREATMENTS

The use of stimulants for the treatment for ADHD, started from 1937 AD, with the use of amphetamine (Benzedrine) by Bradley.[4] In subsequent years, different stimulants and non-stimulants were seen to be effective in the treatment. Stimulants like methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine and lisdexamfetamine were approved by U.S. Food and Drug Administration (FDA). Similarly, non-stimulants like atomoxetine, clonidine, guanfacine were also approved by FDA for the treatment of ADHD. Efficacious medication-based treatments are available and widely used, often alongside complementary psychosocial approaches.[5]

Meta-analysis found that methylphenidate and amphetamine both had moderate to large effect size 0.78 and 1.02 respectively.[6] A meta-analysis of 25 trials of atomoxetine in children with ADHD indicated a moderate effect size (0.64) and trials of long –acting alpha 2 agonist formulations in children indicated medium effect size (0.5-0.6).[7] Despite evidence of good efficacy, these medications do have adverse effects. The long-term outcomes for individuals with ADHD, treated or treatment naïve, is less optimal than those who are unaffected.[8], The other modalities being non-pharmacological therapy, including neuro feedback, neuromodulation, psychotherapy which includes psycho-education, parent training, social skills training, behavior modification, Cognitive Behavior Therapy, Social skills training etc.[9] Studies have demonstrated limited efficacy for most of the non-pharmacological treatments, with small to modest effect sizes for reducing core ADHD symptoms, when applied alone.[10] Multimodal Treatment Study of Children with ADHD (MTA Study) showed that combination of pharmacotherapy and behavior therapy was superior to medication or psychotherapy alone.[11] The therapies were highly efficacious during the clinical trials, but when the cases were transferred back to the community, they were provided less-intense services and the efficacy of the treatment decreased.[12] The limitations of medication treatment for ADHD supports the need for continued search and advancement for novel and improved approaches to its management. Thus, there is always search for new, better and long-lasting modality of treatments, some of which we will be discussing in our review.

RECENT ADVANCES

1. Pharmacotherapy

a. FDA approved in last 3 years

Serdexmethylphenidate: Its combination with dexmethylphenidate (70% and 30% by molar ratio) was approved by FDA in March, 2021, as a single daily dose. It is pharmacologically inactive until converted to the active dexmethylphenidate in the lower intestine.[13] Though stimulant, it has lower abuse potential and less severe adverse effect profile.[14,15,16]

Viloxazine:Previously used as antidepressant, it is a non-stimulant drug, approved by FDA in April, 2021 for use in ADHD.[17] It acts via selectively inhibiting norepinephrine reuptake and has low abuse potential with adverse effects similar to non-stimulants.[18] It is taken once daily and starting dose is 100 mg, optimized to maximum 400 mg.[19]

b. In pipeline

Different other medications are in pipeline at different phases of the clinical trial and the world is hopeful to witness better medication with better efficacy and side effect profile in the future.[20] Some to mention are-

Fasoracetam – Nonselective agonist of all metabotropic glutamate receptors (mGluRs) and effective in the treatment of ADHD in people with specific mGluR mutations.[21]

Dasotraline- Potent inhibitor of dopamine and norepinephrine transporters but does not stimulate dopamine release as stimulant does and has minimal abuse potential. It has long elimination half-life with stable plasma concentrations, requiring once-daily dosing.[22,23]

Tipepidine hibenzate–Non-narcotic antitussive agent with good safety profile.[24]It inhibits G protein-coupled inwardly rectifying potassium channels (GIRK) at ventral tegmental area and locus coeruleus, increasing dopamine and noradrenaline levels in the nucleus accumbens and pre-frontal cortex, resulting in alleviation of ADHD symptoms.[25]

Centanafadine–It is serotonin, norepinephrine and dopamine reuptake inhibitor, and phase III clinical trials showed better efficacy, safety and tolerability.[8,26]

Mazindol - It inhibits reuptake of norepinephrine, dopamine and serotonin and has a weak dopamine releasing property, thus similar to central nervous system stimulant, amphetamine.[27]

Similarly other drugs in the pipeline moving on with trials are Eltoprazine, L-Threonic Acid Magnesium Salt[28],micro-dosing of LSD[29]

2. Psycho-social intervention

Some to mention are behavior management interventions (parent training, classroom interventions, peer-based interventions); training interventions (cognitive training, neurofeedback, organization), cognitive behavior therapy (CBT); physiological treatments (physical activity) and mind-body interventions (meditation, yoga, tai chi, mindfulness, hypnotherapy).[10] These are broad spectrum, where some has proved to be effective, and some other, under research with inconsistent results. Behavioral therapy focuses on the use of operant and classical conditioning, and aims at preventing and reducing the disruptive behaviors.[30] CBT enhances positive behaviors and create situations in which desired behaviors may occur. It has a moderate effect size on improving inattention and anger,

but a small effect size on decreasing impulsivity and hyperactivity in children.[31,32] Several studies have tested whether cognitive training (CT) improves ADHD symptoms.

The majority of studies have tested that effects of working memory (WM) training and found near-transfer effects on WM performance in similar tasks but no far-transfer effects on other cognitive functions such as attention or inhibition or academic performance or on ADHD symptoms or any other clinically relevant measures, like day to day functioning. The same has been found with attention training, which improves the performance of ADHD children on lab-based tasks of attention, but it does not improve behavioral attention which is measured in clinical ADHD symptoms and which is manifested in day to day functions.[33]

It has been argued that CT of many different functions may be more successful. However, even studies that trained several functions like attention, inhibition, switching, planning and WM, all together, did not show any transfer effects on lab-based measures of attention or on ADHD symptoms of attention. This means that CT has a very limited effect of improving the very function that is being trained but it does not transfer to other cognitive functions, to daily life, to academic performance, or to ADHD clinical symptoms. CT hence has shown to have limited 'real-world' ecological validity.[33]

Regulation-Focused Psychotherapy for Children (RFP-C) considers externalizing behaviors as expressions of maladaptive defense mechanisms and provide psycho-education and empathic support to parents in distress.[34] Schema therapy targets to identify and alleviate early maladaptive schemas, internalized assumptions and expectancies, an individual has developed about their own identity in relation to people and world around them.[35] The most studied and evidence-based is the CBT in ADHD.

3. Dietary patterns and nutritional supplements

Different micronutrients are required in the formation of different neurotransmitters in the brain that can prevent the risk of development of ADHD. Junk-food, processed-food, Western-like diet pattern are risk to develop ADHD.[36,37] On contrary, the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH) diet, and vegetarian diets are inversely associated with the risk of ADHD.[38,39] The healthy dietary pattern(fruits and vegetables, fish high in PUFAs and micronutrients) decreases the risk by 37% (OR: 0.63), the Western-type (red and processed meats, refined cereal grains, soft drinks, and hydrogenated fats) increases the risk by 92% (OR: 1.92) while the junk food pattern (processed foods, artificial food coloring and sugar) increases the risk by 51% (OR: 1.51).[40,41]

Vitamin A, B1, B2, C, D, iron,zinc and calcium has shown to be preventive from developing ADHD and even curative in supplementation with other medications.[42] Similar is the effect of poly-unsaturated fatty acids (PUFAs).[43] These findings are not consistent in both the dietary patterns and supplements, and many studies show no statistically significant differences with placebo.[44,40]

4. Gut microbe

The microbiota in the gut aids in production of different neuroactive compounds including neurotransmitters and regulate gene expression, epigenetics and neuroplasticity influencing cognition, emotion and behavior.[45] The link in ADHD between gut, microbiome and brain is established via vagus nerve, their interaction leading to synthesis of neurotransmitters and interaction with the immunological system.[46] Different gut microbes like enterococcus, bifidobacterium, odoribacter, bacteroides, dialister, veillonellaceae were increased and faecalibacterium,ruminococcaceae,anaerotaenia, gracilibacter were decreased, which were responsible for above-mentioned mechanism increasing possibility of ADHD.[47] Thus, there is a possible role of probiotics in ADHD prevention.[48]

5. Digital Therapy

The unequal delivery of available treatments, inability to access health services, side effects of medications and limited pediatric mental health experts for behavioral therapy, have necessitate the requirement of alternate therapy with easy access.[49] Digital health intervention (DHI) has come into play to overcome the shortcomings. FDA has approved game-based digital therapy- "EndeavorRx" in June 2020, for ADHD in 8-12 years children, primarily focusing on treatment of inattentive or combined-type ADHD. This is the first game-based therapeutic device approved by the FDA for any type of medical condition.[50] In addition, other DHIs like, video-games (ACTIVATE™), smartphone apps (RECOGNeyes), wearable technologies might have potential in the treatment of ADHD, which is still under study.[51] As the world is moving towards technology and artificial intelligence, their optimum use in treatment will be inevitable. The possible mechanisms of DHIs in ADHD are increased release of dopamine, increased blood flow, increased brain volume, neuroplasticity of white matter and motivational, emotional and social benefits.[49]

6. Massage therapy

It is an alternative therapy, with different styles of manual manipulations on a subjects' body, like, Thai massage,

Swedish massage,Traditional Chinese Medicine massage (tuina), among others.[52] The mechanism may be due to stimulation of pressure receptors, which enhances vagal activity and reduces cortisol release. It was found efficacious alone or in combination with medications and had better side effect profile than medications.[53] Parent-administered tuina had almost similar beneficial effects in improving core hyperactivity/impulsivity symptoms,appetite and sleep quality.[54]

7. Neurofeedback and brain stimulation

Neurofeedback (NF)

Neurofeedback ,also called Electroencephalographic (EEG) biofeedback or Neurotherapy, is a non-invasive intervention for the treatment of ADHD.[55] NF acts via the principles of operant conditioning and trains participants to self-regulate their brain activity.[56] The advances in NF is the incorporation of functional Magnetic Resonance Imaging (fMRI) and Near-Infrared Spectroscopy (NIRS) techniques, in addition to EEG-NF.[57] fMRI- Neurofeedback has much better spatial resolution and, probably because of this, learning is much faster than for EEG-NF. Another advantage is that due to its spatial resolution, fMRI-NF can target specific brain regions that are abnormal in the patients, and that maybe subcortical (like the basal ganglia) or deep in the frontal cortex (like inferior frontal cortex) which EEG-NF cannot reach. So, fMRI-NF can target the very areas found to be abnormal in their activation in fMRI studies over the past two decades.

So far, only two fMRI-NF studies have been published in ADHD. They found an improvement in attention and working memory task in the NF group but in the clinical symptoms after neurofeedback training. What is most interesting is that the effects of clinical improvements were seen to be more pronounced a year later than immediately after the neurofeedback, suggesting a longer-term neuroplastic effects, which is what makes neurotherapies unique over drugs.[58] The findings for neurofeedback is promising however, studies have shown mixed result in the efficacy of NF in ADHD.[59]

Brain stimulation

Various neuromodulation techniques are used as non-invasive brain stimulation in ADHD treatment. Some to discuss are-

a. external Trigeminal Nerve Stimulation (eTNS): First medical device approved by FDA on 2019, to treat ADHD.[60] It is a cell-phone sized device, used at home, administered by parents or caregivers, where electrodes are attached to the child's forehead and electrical pulses are applied via rechargeable 9-volt lithium battery.[61] It has minimal side-effects, feels like a tingling sensation on the contact skin and it stimulates branches of the trigeminal nerve,which projects to locus coeruleus, thalamus, and cerebral cortex, involved in ADHD.[60]

b. repetitiveTranscranial Magnetic Stimulation (rTMS): It is a non-invasive and relatively safe brain stimulation technique that uses brief, intense pulses of electric current via electromagnetic induction. It stimulates the dysregulated neurocircuits, causes neuroplastic changes and alteration in neurochemicals, thus implicating to ADHD, with minimal side effects.[62] Different studies in children showed that rTMS with atomoxetine was superior to atomoxetine alone or sham rTMS.[63] Further large scale studies are required to generalize the findings.

c. Transcranial Direct Current Stimulation(tDCS): There is application of a weak direct electric current via scalp electrodes and is effective in ADHD treatment.[64] It is much easier to apply and also has lower financial costs and side effects than rTMS. Furthermore, tDCS has the advantage of being less painful than TMS and, hence, is more child-friendly.[65] However, based on current evidences and research, it cannot be stated that tDCS is a valid treatment to improve ADHD symptoms or key performance measures of attention and inhibition.[62]

Other modalities of neuromodulation under study for ADHD are, transcranial random noise stimulation (tRNS), transcranial alternating current stimulation (tACS), transcutaneous supraorbital nerve stimulation (tSNS).[66]

Findings of using these noninvasive brain stimulation methods in ADHD have been mixed. In conclusion, these treatments are very novel in general and, in particular, in their applications to children and to ADHD, and far more research is needed to answer all these clinical questions before we can even think of using it in ADHD clinically.

Nepalese context: Based on the experiences of Child and Adolescent Psychiatrists working at the only Child and Adolescent Psychiatry Unit at Kanti Children's Hospital, Nepal, medications commonly prescribed for ADHD in Nepal are clonidine, atomoxetine and risperidone. Atomoxetine a non stimulant for ADHD was launched in Nepal a year ago. Psychotherapies are also mainstay of treatment where CBT, behavioral therapy, parent training are focused but RFP-C, neurofeedback, mind-body intervention are not in regular practice.

Dietary advice and supplements are advised but no emphasis on gut microbe therapy. "EndeavorRx" as a digital thera-

py is not used and we do not focus on massage therapy. Neuromodulation including rTMS though available but not regularly advocated for the treatment of ADHD in our settings.Unavaiability of stimulant for ADHD in Nepal is a huge concern. Limitations of treatment options, with unavailability of stimulants highlights the pressing need to inform concerned stake holders and policy makers.

CONCLUSION

Within the last three years, two medications were approved by FDA, Viloxazine and Serdexmethylphenidate, a non-stimulant and stimulant respectively. In addition, other drugs are in the pipeline, at II and III phase of clinical trials. FDA has also approved, for the first time, a game-based therapy called "EndeavorRx" and studies are focusing on the use of other DHIs. Neuromodulation therapy in different forms are showing promising results and the FDA has approved eTNS for the treatment of ADHD. Similarly, studies on dietary patterns and nutritional supplements, are directing us to certain diet patterns, like, Mediterranean diet, DASH diet and supplements of zinc, PUFA, vitamins and minerals in addition with medication. Different psycho-social interventions at home, school or community are seen to be effective to manage the symptoms of ADHD.

To conclude, large population-based epidemiological studies are needed in children with ADHD. The longitudinal studies should be conducted to better understand the treatment outcomes in long-term and more randomized controlled trials are needed to assess safety and efficacy of different promising interventions for ADHD.

CONFLICT OF INTEREST:

None

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References

1. Salari N, Ghasemi H, Abdoli N, Rahmani A, Shiri MH, Hashemian AH, et al. The global prevalence of ADHD in children and adolescents: a systematic review and meta-analysis. Ital J Pediatr. 2023 Apr 20;49(1):48.
2. Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology. 2009 Dec;57(7–8):579–89.
3. Barkley RA. Major life activity and health outcomes associated with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002;63 Suppl 12:10–5.
4. Bradley C. THE BEHAVIOR OF CHILDREN RECEIVING BENZEDRINE. AJP. 1937 Nov;94(3):577–85.
5. Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. The Lancet. 2020 Feb;395(10222):450–62.
6. Cortese S, Adamo N, Del Giovane C, Mohr-Jensen C, Hayes AJ, Carucci S, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. The Lancet Psychiatry. 2018 Sep;5(9):727–38.
7. Schwartz S, Correll CU. Efficacy and Safety of Atomoxetine in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder: Results From a Comprehensive Meta-Analysis and Metaregression. Journal of the American Academy of Child & Adolescent Psychiatry. 2014 Feb;53(2):174–87.
8. Mechler K, Banaschewski T, Hohmann S, Häge A. Evidence-based pharmacological treatment options for ADHD in children and adolescents. Pharmacology & Therapeutics. 2022 Feb;230:107940.
9. Voeller KKS. Attention-Deficit Hyperactivity Disorder (ADHD). J Child Neurol. 2004 Oct;19(10):798–814.
10. Sonuga-Barke EJS, Brandeis D, Cortese S, Daley D, Ferrin M, Holtmann M, et al. Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments. AJP. 2013 Mar;170(3):275–89.
11. Jensen PS, Hinshaw SP, Swanson JM, Greenhill LL, Conners CK, Arnold LE, et al. Findings from the NIMH Multimodal Treatment Study of ADHD (MTA): Implications and Applications for Primary Care Providers: Journal of Developmental & Behavioral Pediatrics. 2001 Feb;22(1):60–73.
12. Wolraich ML, Chan E, Froehlich T, Lynch RL, Bax A, Redwine ST, et al. ADHD Diagnosis and Treatment Guidelines: A Historical Perspective. Pediatrics. 2019 Oct 1;144(4):e20191682.
13. Kollins SH, Braeckman R, Guenther S, Barrett AC, Mickle TC, Oh C, et al. A Randomized, Controlled Laboratory Classroom Study of Serdexmethylphenidate and d-Methylphenidate Capsules in Children with Attention-Deficit/Hyperactivity Disorder. Journal of Child and Adolescent Psychopharmacology. 2021 Nov 1;31(9):597–609.
14. Braeckman R, Guenther S, Mickle TC, Barrett AC, Smith A, Oh C. Dose Proportionality and Steady-State Pharmacokinetics of Serdexmethylphenidate/Dexmethylphenidate, a Novel Prodrug Combination to Treat Attention-Deficit/Hyperactivity Disorder. Journal of Child and Adolescent Psychopharmacology. 2022 Jun 1;32(5):288–95.
15. Childress AC, Cutler AJ, Patel M, Oh C. Analysis of Growth Velocity in Children with Attention-Deficit/Hyperactivity Disorder Treated for up to 12 Months with Serdexmethylphenidate/Dexmethylphenidate. Journal of Child and Adolescent Psychopharmacology. 2023 May 1;33(4):134–42.
16. Childress AC, Marraffino A, Cutler AJ, Oh C, Brams MN. Safety and Tolerability of Serdexmethylphenidate/Dexmethylphenidate Capsules in Children with Attention-Deficit/Hyperactivity Disorder: A 12-Month, Open-Label Safety Study. Journal of Child and Adolescent Psychopharmacology. 2023 Mar 1;33(2):51–8.
17. Lamb YN. Viloxazine: Pediatric First Approval. Pediatr Drugs. 2021 Jul;23(4):403–9.
18. Pozzi M, Bertella S, Gatti E, Peeters GGAM, Carnovale C, Zambrano S, et al. Emerging drugs for the treatment of attention-deficit hyperactivity disorder (ADHD). Expert Opinion on Emerging Drugs. 2020 Oct 1;25(4):395–407.
19. Edinoff AN, Akuly HA, Wagner JH, Boudreaux MA, Kaplan LA, Yusuf S, et al. Viloxazine in the Treatment of Attention Deficit Hyperactivity Disorder. Front Psychiatry. 2021 Dec 17;12:789982.
20. Childress AC, Beltran N, Supnet C, Weiss MD. Reviewing the role of emerging therapies in the ADHD armamentarium. Expert Opinion on Emerging Drugs. 2021 Jan 2;26(1):1–16.
21. Elia J, Ungal G, Kao C, Ambrosini A, De Jesus-Rosario N, Larsen L, et al. Fasoracetam in adolescents with ADHD and glutamatergic gene network variants disrupting mGluR neurotransmitter signaling. Nat Commun. 2018 Jan 16;9(1):4.
22. Chen YL, Skende E, Lin J, Yi Y, Wang PL, Wills S, et al. Absorption, distribution, metabolism, and excretion of [14 C]-dasotraline in humans. Pharmacol Res Perspect. 2017 Feb;5(1):e00281.
23. Findling RL, Adler LA, Spencer TJ, Goldman R, Hopkins SC, Koblan KS, et al. Dasotraline in Children with Attention-Deficit/Hyperactivity Disorder: A Six-Week, Placebo-Controlled, Fixed-Dose Trial. Journal of Child and Adolescent Psychopharmacology. 2019 Mar;29(2):80–9.
24. Honda S, Kawaura K, Soeda F, Shirasaki T, Takahama K. The potent inhibitory effect of tipepidine on marble-burying behavior in mice. Behavioural Brain Research. 2011 Jan;216(1):308–12.
25. Dehbozorghi S, Bagheri S, Moradi K, Shokraee K, Mohammadi M, Akhondzadeh S. Efficacy and safety of tipepidine as adjunctive therapy in children with attention-deficit/hyperactivity disorder: Randomized, double-blind, placebo-controlled clinical trial. Psychiatry ClinNeurosci. 2019 Nov;73(11):690–6.
26. Bymaster FP, Golembiowska K, Kowalska M, Choi YK, Tarazi FI. Pharmacological characterization of the norepinephrine and dopamine reuptake inhibitor EB-1020: Implications for treatment of attention-deficit hyperactivity disorder. Synapse. 2012 Jun;66(6):522–32.
27. Abad V, Guilleminault C. New developments in the management of narcolepsy. NSS. 2017 Mar;Volume 9:39–57.
28. Surman C, Vaudreuil C, Boland H, Rhodewalt L, DiSalvo M, Biederman J. L-Threonic Acid Magnesium Salt Supplementation in ADHD: An Open-Label Pilot Study. Journal of Dietary Supplements. 2021 Mar 4;18(2):119–31.
29. Haijen ECHM, Hurks PPM, Kuypers KPC. Microdosing with psychedelics to self-medicate for ADHD symptoms in adults: A prospective naturalistic study. Neuroscience Applied. 2022;1:101012.
30. Pelham WE, Burrows-MacLean L, Gnagy EM, Fabiano GA, Coles EK, Wymbs BT, et al. A Dose-Ranging Study of Behavioral and Pharmacological Treatment in Social Settings for Children with ADHD. J Abnorm Child Psychol. 2014 Aug;42(6):1019–31.
31. Evans SW, Owens JS, Bunford N. Evidence-Based Psychosocial Treatments for Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. Journal of Clinical Child & Adolescent Psychology. 2014 Jul;43(4):527–51.
32. Lee AH, DiGiuseppe R. Anger and aggression treatments: a review of meta-analyses. Current Opinion in Psychology. 2018 Feb;19:65–74.
33. Cortese S, Ferrin M, Brandeis D, Buitelaar J, Daley D, Dittmann RW, et al. Cognitive Training for Attention-Deficit/Hyperactivity Disorder: Meta-Analysis of Clinical and Neuropsychological Outcomes From Randomized Controlled Trials. Journal of the American Academy of Child & Adolescent Psychiatry. 2015 Mar;54(3):164–74.
34. Di Giuseppe M, Prout TA, Rice T, Hoffman L. Regulation-Focused Psychotherapy for Children (RFP-C): Advances in the Treatment of ADHD and ODD in Childhood and Adolescence. Front Psychol. 2020 Nov 3;11:572917.
35. Lücke C. New psychotherapeutic approaches in adult ADHD - acknowledging biographical factors. J NeurolNeuromedicine. 2017 Jul 1;2(7):6–10.

36. Shareghfarid E, Sangsefidi ZS, Salehi-Abargouei A, Hosseinzadeh M. Empirically derived dietary patterns and food groups intake in relation with Attention Deficit/Hyperactivity Disorder (ADHD): A systematic review and meta-analysis. Clinical Nutrition ESPEN. 2020 Apr;36:28–35.
37. Howard AL, Robinson M, Smith GJ, Ambrosini GL, Piek JP, Oddy WH. ADHD Is Associated With a "Western" Dietary Pattern in Adolescents. J AttenDisord. 2011 Jul;15(5):403–11.
38. Khoshbakht Y, Moghtaderi F, Bidaki R, Hosseinzadeh M, Salehi-Abargouei A. The effect of dietary approaches to stop hypertension (DASH) diet on attention-deficit hyperactivity disorder (ADHD) symptoms: a randomized controlled clinical trial. Eur J Nutr. 2021 Oct;60(7):3647–58.
39. Lange KW, Nakamura Y, Reissmann A. Diet and food in attention-deficit hyperactivity disorder. Journal of Future Foods. 2022 Jun;2(2):112–8.
40. Azadbakht L, Esmaillzadeh A. Dietary patterns and attention deficit hyperactivity disorder among Iranian children. Nutrition. 2012 Mar;28(3):242–9.
41. Yan S, Cao H, Gu C, Ni L, Tao H, Shao T, et al. Dietary patterns are associated with attention-deficit/hyperactivity disorder (ADHD) symptoms among preschoolers in mainland China. Eur J ClinNutr. 2018 Nov;72(11):1517–23.
42. Gan J, Galer P, Ma D, Chen C, Xiong T. The Effect of Vitamin D Supplementation on Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of Child and Adolescent Psychopharmacology. 2019 Nov 1;29(9):670–87.
43. Chang JPC, Su KP, Mondelli V, Pariante CM. Omega-3 Polyunsaturated Fatty Acids in Youths with Attention Deficit Hyperactivity Disorder: a Systematic Review and Meta-Analysis of Clinical Trials and Biological Studies. Neuropsychopharmacol. 2018 Feb;43(3):534–45.
44. Carucci S, Romaniello R, Demuru G, Curatolo P, Grelloni C, Masi G, et al. Omega-3/6 supplementation for mild to moderate inattentive ADHD: a randomised, double-blind, placebo-controlled efficacy study in Italian children. Eur Arch Psychiatry ClinNeurosci. 2022 Dec;272(8):1453–67.
45. Morais LH, Schreiber HL, Mazmanian SK. The gut microbiota–brain axis in behaviour and brain disorders. Nat Rev Microbiol. 2021 Apr;19(4):241–55.
46. Keita ÅV, Söderholm JD. The intestinal barrier and its regulation by neuroimmune factors: Intestinal barrier and neuroimmune regulation. Neurogastroenterology& Motility. 2010 Feb 8;22(7):718–33.
47. Shirvani-Rad S, Ejtahed HS, EttehadMarvasti F, Taghavi M, Sharifi F, Arzaghi SM, et al. The Role of Gut Microbiota-Brain Axis in Pathophysiology of ADHD: A Systematic Review. J AttenDisord. 2022 Nov;26(13):1698–710.
48. Pärtty A, Kalliomäki M, Wacklin P, Salminen S, Isolauri E. A possible link between early probiotic intervention and the risk of neuropsychiatric disorders later in childhood: a randomized trial. Pediatr Res. 2015 Jun;77(6):823–8.
49. Pandian GSB, Jain A, Raza Q, Sahu KK. Digital health interventions (DHI) for the treatment of attention deficit hyperactivity disorder (ADHD) in children - a comparative review of literature among various treatment and DHI. Psychiatry Research. 2021 Mar;297:113742.
50. Canady VA. FDA approves first video game Rx treatment for children with ADHD. Mental Health Weekly. 2020 Jun 29;30(26):1–7.
51. Hollis C, Falconer CJ, Martin JL, Whittington C, Stockton S, Glazebrook C, et al. Annual Research Review: Digital health interventions for children and young people with mental health problems - a systematic and meta-review. J Child PsycholPsychiatr. 2017 Apr;58(4):474–503.
52. Chen SC, Yu BYM, Suen LKP, Yu J, Ho FYY, Yang JJ, et al. Massage therapy for the treatment of attention deficit/hyperactivity disorder (ADHD) in children and adolescents: A systematic review and meta-analysis. Complementary Therapies in Medicine. 2019 Feb;42:389–99.
53. Ni X, Zhang-James Y, Han X, Lei S, Sun J, Zhou R. Traditional Chinese Medicine in the Treatment of ADHD. Child and Adolescent Psychiatric Clinics of North America. 2014 Oct;23(4):853–81.
54. Chen SC, Yu J, Wang HS, Wang DD, Sun Y, Cheng HL, et al. Parent-administered pediatric Tuina for attention deficit/hyperactivity disorder symptoms in preschool children: A pilot randomized controlled trial embedded with a process evaluation. Phytomedicine. 2022 Jul;102:154191.
55. Monastra VJ, Lynn S, Linden M, Lubar JF, Gruzelier J, LaVaque TJ. Electroencephalographic Biofeedback in the Treatment of Attention-Deficit/Hyperactivity Disorder. ApplPsychophysiol Biofeedback. 2005 Jun;30(2):95–114.
56. Neuhäußer AM, Bluschke A, Roessner V, Beste C. Distinct effects of different neurofeedback protocols on the neural mechanisms of response inhibition in ADHD. Clinical Neurophysiology. 2023 Sep;153:111–22.
57. Patil AU, Madathil D, Fan YT, Tzeng OJL, Huang CM, Huang HW. Neurofeedback for the Education of Children with ADHD and Specific Learning Disorders: A Review. Brain Sciences. 2022 Sep 14;12(9):1238.
58. Alegria AA, Wulff M, Brinson H, Barker GJ, Norman LJ, Brandeis D, et al. Real-time fMRI neurofeedback in adolescents with attention deficit hyperactivity disorder: Real-Time fMRI-NF in Adolescents with ADHD. Hum Brain Mapp. 2017 Jun;38(6):3190–209.
59. Rahmani E, Mahvelati A, Alizadeh A, Mokhayeri Y, Rahmani M, Zarabi H, et al. Is neurofeedback effective in children with ADHD? A systematic review and meta-analysis. Neurocase. 2022 Jan 2;28(1):84–95.
60. Canady VA. FDA approves marketing of first nondrug treatment for ADHD. Mental Health Weekly. 2019 Apr 29;29(17):3–4.
61. Huus CML, Edemann-Callesen H, Darling-Rasmussen P, Martinsen ØG, Bikic A, Storebø OJ. The use of external Trigeminal Nerve Stimulation as an initial treatment for ADHD symptoms in children: A qualitative study of case series reports. Psychiatry Research Case Reports. 2023 Jul;100154.
62. Rubia K. Cognitive Neuroscience of Attention Deficit Hyperactivity Disorder (ADHD) and Its Clinical Translation. Front Hum Neurosci. 2018 Mar 29;12:100.
63. Nagy NAS, Amin GR, Khalil SA, Mahmoud DAM, Elkholy H, Shohdy M. The therapeutic role of repetitive transcranial magnetic stimulation in children with attention deficit/hyperactivity disorder in Egypt a randomized sham controlled clinical trial. Middle East Curr Psychiatry. 2022 Dec;29(1):55.
64. Nejati V, Salehinejad MA, Nitsche MA, Najian A, Javadi AH. Transcranial Direct Current Stimulation Improves Executive Dysfunctions in ADHD: Implications for Inhibitory Control, Interference Control, Working Memory, and Cognitive Flexibility. J AttenDisord. 2020 Nov;24(13):1928–43.
65. Zewdie E, Ciechanski P, Kuo HC, Giuffre A, Kahl C, King R, et al. Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations. Brain Stimulation. 2020 May;13(3):565–75.
66. Rubia K, Westwood S, Aggensteiner PM, Brandeis D. Neurotherapeutics for Attention Deficit/Hyperactivity Disorder (ADHD): A Review. Cells. 2021 Aug 21;10(8):2156.