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ADHD

Mindfulness Interventions for ADHD: Neurobiologic Antidote?

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Attention deficit hyperactivity disorder (ADHD) has an estimated prevalence in the United States of 9.4% in children and 4.4% in adults.[1] The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* requires that a child, adolescent, or adult with ADHD demonstrates a persistent pattern of inattention and/or hyperactivity/impulsivity that is significantly disruptive, interferes with normal functioning, and is inappropriate for the individual's stage of development.[2] The standard-of-care treatment for both pediatric and adult patients consists of behavioral and psychotherapeutic interventions first (including interventions for parents/family of children with ADHD), followed by medication treatment when behavioral interventions fail to adequately improve symptoms and function.[3] An estimated 64% of children diagnosed with ADHD are prescribed medication for the condition, usually amphetamine-class stimulants or methylphenidate. Adult use of ADHD psychostimulant medication continues to rise.[4] Both adults and children with ADHD diagnoses also may have coexisting conditions: depression, anxiety, learning disabilities, and conduct disorders are common. Untreated ADHD symptoms and coexisting conditions commonly interfere with school, learning, relationships, and work. Thus, the disorder exacts a large toll on individual patients, their families, and the healthcare system in general. The economic impact of child and adult ADHD in the United States has been estimated to range from $146 billion to $266 billion in "excess costs." Those costs are associated with the healthcare, educational, and judicial systems and are related to losses at work via productivity and income.[5]

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Summary Points

- Attention deficit hyperactivity disorder (ADHD) exacts a significant toll on patients and their families, causing disruption of function and relationships at work and school. The economic burden of ADHD and costs related to decreased productivity are significant.
- The current standard of care consists of behavioral interventions and stimulant medication; however, symptoms often are recalcitrant to these therapies and medication treatment has significant potential for undesirable effects.
- Functional neuroimaging studies support the premise that functional connectivity abnormalities in ADHD brains may be targeted directly and improved by mindfulness and meditation interventions.
- A variety of mindfulness and meditation interventions appear to be effective for improving ADHD symptoms of inattention and hyperactivity/impulsivity for adult and pediatric patients.

PATHOPHYSIOLOGY AND BASIC SCIENCE RESEARCH

Approximately one in five patients diagnosed with ADHD in childhood continues to have symptoms into adulthood. Thus, the natural history of the disorder suggests that central nervous system maturation processes mitigate symptoms in most patients. Modern neuroimaging technologies provide some insight into the neuropathophysiology of ADHD. No single anatomical area appears responsible for the ADHD symptom complex. Instead, neuroimaging research consistently demonstrates impaired functional activity and connectivity between several cortical and subcortical brain regions and networks. There are individual differences in these functional neuroimaging findings among ADHD patients, with some patients demonstrating greater cortical dysfunction and some demonstrating greater subcortical dysfunction, helping to explain varying clinical presentations and coexisting conditions.[6-8]

See Table 1 for a comparison of brain areas and networks that appear to be commonly affected in ADHD and their known or hypothesized functions.[6-9] Psychostimulants prescribed for ADHD increase central dopamine and norepinephrine, targeting executive and attentional functioning, and presumably altering activity in associated brain regions and networks. However, these medications have potential for significant adverse effects, for addiction if misused, and for diversion for nonmedical purposes. Recent Cochrane reviews of amphetamine and methylphenidate for ADHD concluded that the risk of adverse effects is significant and evidence for effectiveness is weak, primarily caused by methodologic flaws in existing studies and a lack of robust, randomized, double-blind, placebo-controlled studies.[10,11] It can be argued that the ideal treatment for ADHD — one that has strong evidence of efficacy and low or no risk of harm — has yet to be discovered. Further, since brain maturation alone seems to resolve ADHD manifestations for most individuals, is there a way to harness the brain's innate capacity for neuroplasticity with interventions and practices that kindle natural maturational processes?

When behavioral interventions work to manage ADHD symptoms, it is likely that at least part of their efficacy is due to therapeutic effects on neural functioning. Starting with the seminal functional magnetic resonance imaging (MRI) research of Richard Davidson, PhD, at University of Wisconsin,[12] mindfulness-based and other meditation practices have been shown to alter function in some of the same regions and neural networks affected by ADHD. These functional changes include increased metabolism, blood flow to prefrontal areas, increased mass in areas involved in attention switching and perception of bodily state, increased metabolic rate in frontal and parietal circuits associated with attention, increased activity in the prefrontal executive (dorsolateral prefrontal cortex) and anterior cingulate attentional circuits, and increased cohesiveness of brain electrical activity. The default mode network (DMN) and central executive network (CEN) appear to be important

Table 1. Brain Networks, Function, and Dysfunction in ADHD			
Network	**Anatomic Regions**	**Known/Hypothesized Function**	**Changes in ADHD**
Central Executive Network (CEN)	Frontoparietal, dorsolateral PFC	Organization and planning, value-based decision making	Hypoactive, decreased functional connections to SN and DMN
Ventral Attention Network (VAN)	Temporoparietal junction, supramarginal gyrus, frontal operculum, anterior insula	Directing attention to salient stimuli, excluding irrelevant stimuli and background noise	Hypoactive
Dorsal Attention Network (DAN)	Interparietal sulcus, frontal eye field	Selecting external stimuli that are compatible with personal goals and experience	Overactive
Default Mode Network (DMN)	Anterior medial PFC, posterior cingulate cortex, dorsomedial PFC subsystem, medial temporal lobe subsystem	Daydreaming, mind wandering, contemplating, reflecting on oneself; deactivates when engaging in a task	Persistently overactive, inability to "switch off", decreased functional connections to DMN/CEN
Salience Network (SN)	Anterior insula, dorsal anterior cingulate cortex, amygdala, ventral striatum, substantia nigra/ventral tegmentum	Selecting stimuli deserving of attentional focus and coordinating neural responses to them; modulating switch between DMN and CEN	Decreased functional connections to DMN/CEN
Reward System	Striatum, anterior cingulate cortex and orbitofrontal cortex, dorsolateral prefrontal cortex	Reward anticipation and processing, balancing short-term rewards with risks and long-term goals	Exaggerated neuro-functional activity in response to negative and positive emotional and reward stimuli
ADHD: attention deficit hyperactivity disorder; PFC: prefrontal cortex			

both in ADHD-related pathogenesis (*see Table 1*) and in brain changes associated with meditation practice. DMN activity typically is increased when one's brain is in a "resting" state and has no specific task to perform. Activation of the DMN is typified by mind-wandering or daydreaming, and activity can be "switched off" rapidly when an individual needs to attend to a specific task or object. In ADHD, DMN activity tends to be increased at baseline and does not switch off and on rapidly and readily in response to external attentional demands. The CEN is involved in connections between the DMN and the CEN and facilitates the rapid switches from "resting" to attentively focused states as needed. Meditation studies in normal and ADHD subjects suggest that functional activity within the DMN and CEN decrease and increase respectively, and connections between the DMN and CEN increase both in active meditation (state) and as long-term consequences of meditation practice (trait), precisely the opposite of the activity changes associated with ADHD.[13-18] EEG changes associated with ADHD include abnormal ratios of theta, beta, and alpha waveform activity, as well as decreased coherence of specific waveform frequencies across brain regions.[19] Again, meditation practices in normal subjects appear to move brainwave activity and coherence in directions opposite to those observed in ADHD-diagnosed individuals. Thus, meditation interventions, which typically are low-cost and low-risk, may be entirely rational for addressing ADHD symptoms.

CLINICAL STUDIES ON MINDFULNESS AND MEDITATION PRACTICES FOR ADHD

A 2010 Cochrane systematic review included four studies of meditation-type interventions for childhood ADHD, two of which were doctorate dissertations from 1984 and 1987. The authors included two peer-reviewed, published studies in their review and determined that the quality of evidence was "very low" according to the GRADE classification. In addition, there was insufficient evidence to draw conclusions about the effectiveness (or risk of side effects) of meditation as an intervention for ADHD.[20]

Zhang et al conducted a 2018 meta-analysis of randomized, controlled trials of mindfulness and meditation-based interventions for ADHD in children/adolescents (six studies between 2004 and 2017) and adults (six studies between 2015 and 2018). Effect sizes of the interventions were determined from pooled data for the primary outcome of ADHD core symptoms of inattention plus hyperactivity/impulsivity reported together and on inattention and hyperactivity/impulsivity when reported separately. When only inattention or impulsivity/hyperactivity were the reported outcomes, these were used as the primary outcome. The analyses demonstrated statistically

Table 2. Comparison of Effect Sizes for Heterogeneous Trials of Mindfulness/ Meditation Practices for ADHD in Children/ Adolescents and Adults

	Study Author (Year)	Hedge's g (effect size), 95% CI, *P* Value
Children/ Adolescents	Jensen (2004)	-0.23; -1.11 to 0.64; *P* = 0.60
	Haffner (2006)	-0.74; -1.64 to 0.16; *P* = 0.11
	Kim (2014)	-1.02; -1.91 to -0.12; *P* = 0.03
	Sidhu (2015)	-0.44; -1.05 to 0.38; *P* = 0.35
	Gershy (2017)	-0.10; -0.62 to 0.42; *P* = 0.71
	Lo (2017)	-0.54; -0.94 to -0.14; *P* = 0.01
	Pooled Data Analysis	-0.44; -0.69 to -0.19; *P* = 0.00
Adults	Fleming (2015)	-0.46; -1.13 to 0.22; *P* = 0.19
	Mitchell (2017)	-1.95; -2.99 to -0.92; *P* = 0.00
	Petterson (2017)	-0.78; -1.50 to -0.06; *P* = 0.03
	Hoxhaj (2018)	0.24; -0.19 to 0.67; *P* = 0.28
	Janssen (2018)	-0.26; -0.62 to 0.09; *P* = 0.15
	Gu (2018)	-1.28; -1.86 to -0.70; *P* = 0.00
	Pooled Data Analysis	-0.66; -1.21 to -0.11; *P* = 0.02

CI: confidence interval
Adapted from Zhang J, Díaz-Román A, Cortese S. Meditation-based therapies for attention-deficit/hyperactivity disorder in children, adolescents and adults: A systematic review and meta-analysis. *Evid Based Ment Health* 2018;21:87-94.

significant effect sizes for the interventions for reducing ADHD symptoms compared to controls.[21] (*See Table 2.*)

In 2017, Evans et al conducted a systematic review of a wider range of studies of meditation-based interventions for children with ADHD. This review of 16 studies included various study designs (one RCT, case studies, single-arm studies, and various active, inactive, and waitlist controls) and interventions (meditation, yoga, mindfulness martial arts, and other mindfulness-based programs). They measured and compared effect sizes, which were found to be significant for improving ADHD core symptoms. However, the overall risk of bias in all studies was deemed serious to critical because of methodologic flaws, including uncontrolled single-arm studies, small sample sizes, use on non-validated measures, lack of blinding, selection bias, and failure to account for subject attrition and missing data.[22]

In 2019, Poissant et al published a review and meta-analysis that included four of the adult trials reviewed by Zhang et al. Again, mindfulness-based interventions appeared to be beneficial for reducing ADHD symptoms in adults with significant effect sizes for most studies.[23] However, all but one study (Janssen et al; 2018[24]) had significant risk of bias due to flawed study design.

Details from the study by Janssen et al are discussed here because of their unique standing among the current literature as a well-powered, multicenter, single-blind, RCT of mindfulness-based cognitive therapy (MBCT) for adult ADHD that included follow-up assessments. The intervention group received MBCT (eight 2.5-hour weekly sessions including sitting meditation, body scan, and mindful movement; a six-hour silent retreat; psychoeducation, cognitive behavioral therapy [CBT] techniques and group discussions; and treatment as usual [TAU]). Control group subjects received TAU only, inclusive of medication and behavioral support. A clinician blinded to subject allocation administered the Conners' Adult ADHD Rating Scale (CAARS) at baseline and post-treatment to assess the effect of the intervention on ADHD symptoms overall and subset symptoms of inattention and hyperactivity/impulsivity as a primary outcome. Secondary outcomes were obtained by self-report during the post-treatment follow-up intervals using CAARS and additional validated instruments to measure executive function, mindfulness skills, positive mental health, self-compassion, and general functioning. A significant reduction in clinician-rated ADHD symptoms was noted post-treatment in this study in MBCT and TAU subjects (mean difference, -3.44; 95% confidence interval, -5.75 to -1.11; P = 0.004; d = 0.41), and this effect was maintained at six months' follow-up. MBCT and TAU patients also demonstrated more improvements in secondary outcomes compared to TAU controls, both post-treatment and at six months' follow-up.

Aadil et al published a narrative review of 16 MBCT interventions for adult ADHD. [25] Although they stated that the 12 most recent studies (2012-2017) all demonstrated small to significant symptom reductions, there were no statistical analyses included in the review for evaluating and comparing effect sizes in these studies. Of note, three of the six RCTs in the meta-analysis by Zhang et al were included in the review by Aadil et al.

Other reviewers of existing published mindfulness/ meditation interventions for ADHD for adults and children, with or without other adjunctive therapies, have arrived at similar conclusions.[26-29]

CONCLUSION AND RECOMMENDATIONS

Few controlled trials of the effects of mindfulness and meditation interventions for ADHD in children and adult populations have been published since the Cochrane review in 2010. Of the published trials, the prevailing outcomes suggest that mindfulness practices and meditation are effective interventions for ADHD and result in symptom improvement, although all studies to date are hampered by methodological weaknesses resulting in significant risk of bias. Further, study interventions are quite heterogeneous (e.g., incorporating elements of mindfulness or meditation with cognitive behavioral therapy, yoga, martial arts, or parent and family therapy), making it difficult to discern the contribution of the mindfulness-based/meditation interventions to treatment effect. The neural correlates of the ADHD symptom complex and the neurobiology of a meditation practice suggest that the latter may be a functional "antidote" for the brain network dysfunctions associated with ADHD symptoms.

Well-constructed, methodologically robust controlled trials that demonstrate statistically and clinically significant effectiveness are needed before meditation practices can be considered standard care. Though the expense of mindfulness-based courses may be limiting for some individuals, MBCT is covered by most insurance plans that include mental health and group therapy benefits. Further, several popular free or low-cost mindfulness and meditation digital applications teach basic principles and help guide a beginner's practice. Whilst awaiting evidence from additional clinical studies, mindfulness and meditation interventions for ADHD (especially MBCT) can be endorsed for ADHD patients and their families who are interested and motivated, based on treatment potential, low risk, and demonstrated salubrious effects on mental health and well-being. ■

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WEIGHT MANAGEMENT

ABSTRACT & COMMENTARY

Using Apple Cider Vinegar for Weight Management on a Restricted Diet

By Jessica Orner, MD

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Dr. Orner reports no financial relationships relevant to this field of study.

SYNOPSIS: Supplementation with 30 mL of apple cider vinegar combined with a restricted calorie diet may decrease body weight, body mass index, and serum triglyceride levels in people with obesity.

SOURCE: Khezri SS, Saidpour A, Hosseinzadeh N, Amiri Z. Beneficial effects of apple cider vinegar on weight management, visceral adiposity index and lipid profile in overweight or obese subjects receiving restricted calorie diet: A randomized clinical trial. *J Funct Foods* 2018;43:95-102.

Apple cider vinegar (ACV) has many uses in today's society. An internet search of ACV will yield more than 17 million results, with articles ranging from food preparation to weight loss to facial toning.[1] Although vinegar has been used for centuries as a home remedy, there is a paucity of research supporting many of the claims for ACV.

In a 2009 randomized, controlled trial from Japan, researchers demonstrated that body weight, body mass index (BMI), and serum triglycerides lowered significantly in participants with obesity who ingested 15-30 mL of ACV vs. a placebo group.[2] The weight management benefits of vinegar are postulated to be due to acetic acid suppressing fat accumulation and appetite suppression due to nausea.

In this randomized clinical trial conducted from October to December of 2014, Khezri et al compared the effects of a restricted calorie diet (RCD) with 30 mL per day of ACV to a control group who had an RCD only. The RCD included a 250 kcal/day energy deficit. The primary outcome was dietary modification in response to ACV ingestion.[3] Secondary outcomes were anthropometric changes: plasma triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C). The researchers assessed plasma concentrations of neuropeptide-Y (NPY), which is known to stimulate the appetite,[4] to determine the effects of ACV on NPY.

The researchers selected participants using convenience sampling from a population at the Specialized Clinic of Nutrition and Diet Therapy in Tehran, Iran. Forty-four overweight or obese adults with BMIs ranging from 27-40 kg/m^2 were eligible. Of the eligible participants, two in the ACV group and three in the control group were excluded because of their inability to cooperate or medical treatments. Patients also were excluded for regular consumption of ACV within one month prior to the start of the study. The researchers noted that the enrolled subjects did not have infectious diseases, thyroid disorders, diabetes, or gastrointestinal diseases.[3]

The intervention was conducted over 12 weeks. The test group received 30 mL of ACV divided into 15 mL at lunch with salad and 15 mL at dinner. Both the control

Summary Points

- Both the study and control groups followed a restricted calorie diet with a 250 kcal/day energy deficit. The study group received 30 mL of apple cider vinegar divided into15 mL at lunch and dinner.
- There was a statistically significant reduction in body fat and body mass index (BMI) in both groups, with a statically significant reduction in triglycerides, body weight, BMI, and hip girth in the study group compared to the control.
- There were no significant between-group differences in energy intake or physical activity.

Table 1. Changes for Apple Cider Vinegar vs. Control Group			
Variable	**Baseline**	**Week 12**	**Change**
Body Weight			
ACV	83.4 ± 16	79.5 ± 15	-4 ± 2.5 (*P* = 0.001)
Control	82 ± 14	79.5 ± 14	-2.3 ± 1.6 (*P* = 0.01)
Body Mass Index (kg/m^2)			
ACV	32 ± 5.3	30.34 ± 5.15	-1.52 ± 0.9 (*P* = 0.001)
Control	32.2 ± 4.5	31.37 ± 4.65	-0.89 ± 0.6 (*P* = 0.001)
Hip (cm)			
ACV	113.13 ± 8.31	107.59 ± 8.84	-5.9 ± 3.71 (*P* = 0.001)
Control	113.12 ± 12.07	109.7 ± 10.25	-3.37 ± 2.49 (*P* = 0.001)
Triglycerides			
ACV	205.04 ± 22	146.95 ± 12	-58.1 ± 16 (*P* = 0.002)
Control	142.55 ± 12	187.55 ± 28	45 ± 19.8 (*P* = 0.03)
ACV: apple cider vinegar			

group and the group receiving ACV followed an RCD. The RCD was determined by subtracting 250 kcal from the participant's estimated energy requirements per day based on the Mifflin-St. Jeor equation, and was designed to provide 55% carbohydrates, 30% fats, and 15% protein. This equation estimates the resting metabolic rate using mass, height, and age. The authors of a 2005 systematic review that compared four predictive equations for resting metabolic rate noted that the Mifflin-St. Jeor equation was more likely than other equations to estimate resting metabolic rate to within 10% of measured rates.[5]

Several measurements were taken at baseline, six weeks, and 12 weeks. These included anthropometric data, physical activity, and an appetite score using the Simplified Nutritional Appetite Questionnaire (SNAQ). A three-day dietary recall was completed at baseline, week 6, and week 12 to estimate caloric intake. This dietary recall provided information about any dietary adjustments that participants made during the trial. Fasting blood samples were collected at baseline and at the end of week 12, measuring triglycerides, total cholesterol, HDL-C, and plasma NPY concentrations. There was no information on adverse events during the study.

There were no significant differences between groups in regard to energy intake or physical activity. Both groups had a reduction in their energy intake at the end of the 12 weeks when compared to baseline. However, the reduction for the control group was not significant (*P* = 0.12). The ACV group did have a significant reduction in dietary energy intake at 12 weeks when compared to baseline (*P* = 0.01), with a significant decrease in intake of saturated fatty acids and monounsaturated fatty acids (*P* = 0.03). There was not a significant difference between the groups in protein, carbohydrate, or cholesterol intake.

Both the ACV and control group had a significant reduction in body fat and BMI from baseline (*P* = 0.001). When comparing the ACV and control groups, there was a significant reduction in hip circumference and body weight, with the ACV group losing an average of 4 kg and the control group losing an average of 2.3 kg. (*See Table 1.*)

The ACV group had a reduction in plasma triglycerides at week 12 when compared to baseline and the control group (*P* = 0.001). Concurrently, the control group had a significant increase in triglycerides compared to baseline (*P* = 0.035). There were no statistically significant changes in LDL-C or NPY.

Compared to the control group, the ACV group had a reduced SNAQ score at the end of 12 weeks (*P* = 0.04), suggesting a decrease in appetite.

■ COMMENTARY

As the popularity of ACV increases, additional research on its effectiveness in weight management is helpful. These authors showed that the group consuming ACV and following an RCD had a reduction in body weight, saturated fatty acid intake, and plasma triglycerides compared to the control group following only an RCD. They also showed that while the SNAQ score of the control group stayed at approximately 14.5, the ACV SNAQ score decreased to an average of approximately 12.9.

However, there are several concerns with this study. The researchers were not able to blind the study subjects because of the strong taste and odor of ACV. This introduces the potential for bias related to participants knowing they are in the study group. Also, ACV is postulated to have health effects from both acetic acid and antioxidation from polyphenolic compounds.[6] In this study, the ACV was sourced from traditional medicine stores in Tehran and was prepared by combining 3 kg of apples with 1 kg of white vinegar and storing for 30 days. This differs from other methods, which involve combining apples with sugar and water and allowing them to ferment for six to eight weeks. This difference in processing could lead to changes in polyphenol composition.[7] It is unclear if this would affect the overall effects on weight management.

Another factor to consider was the sample size and sampling method. The researchers selected participants using convenience sampling. Although this type of sampling is cost-effective and easier than other options, it increases the risk of sampling error and underrepresentation of subgroups in a population. It limits our ability to generalize these results to larger or more diverse populations.

In regard to adverse events, the risk of adding ACV to the diet is likely lower than other weight loss interventions, such as pharmaceutical medication. However, the authors did not provide information on adverse events. ACV can affect tooth enamel and lead to nausea. It would be useful information to note the adverse effects in future studies so clinicians can offer patients comprehensive counseling on the risks and benefits of the treatment.

Overall, studies addressing these concerns are needed before changing clinical practice to recommend ACV with a restricted diet as a weight management option. ■

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CME QUESTIONS

1. **Which of the following best describes neuropathophysiology in patients diagnosed with ADHD compared to healthy controls, based on recent functional imaging studies?**
   a. Reduced cortical volume
   b. Altered activity within and connectivity between executive, salience, and default networks
   c. Altered proportions of theta, beta, and alpha brainwaves
   d. Underactive executive network
2. **In the study by Khezri et al, participants in the apple cider vinegar group had a statistically significant reduction in which of the following?**
   a. High-density lipoprotein cholesterol
   b. Physical activity
   c. Body mass index
   d. Plasma concentration of neuropeptide-Y
3. **In the Khezri et al study, the restricted calorie diet was designed to have:**
   a. a 250 kcal/day energy deficit, 55% carbohydrates, 30% fats, and 15% protein.
   b. a 500 kcal/day energy deficit, 60% fats, 20% carbohydrates, 20% protein.
   c. a 250 kcal/day energy deficit, 60% fats, 20% carbohydrates, 20% protein.
   d. a 500 kcal/day energy deficit, 55% carbohydrates, 30% fats, 15% protein.

[IN FUTURE ISSUES]

Short- and Long-Term Effects of Cannabis for Headaches and Migraines

Cannabinoids for Treating Mental Health Disorders