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Review of Treatments for ADHD and the Evidence Behind Them

**Written by members of the Pediatric Interest Professional Affairs
Committee of the New York State Association of Neuropsychology (NYSAN)**

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Summary

Attention-Deficit/Hyperactivity Disorder (ADHD) is the most common childhood psychiatric disorder and carries significant impact on functional outcomes for children and adults. Children with ADHD are significantly more likely to endure academic, psychosocial, and behavioral problems as adults, and have higher rates of other comorbid disorders. As such, identifying the most appropriate treatments is crucial in helping those with ADHD achieve the best functional outcomes. While medication treatment has been one of the most studied treatments for ADHD, the understandable reluctance many parents exhibit with regard to medication treatment, as well as the fact that not all children respond to stimulant medication, has spurred many to look at alternative ways of treating the core symptoms of ADHD. As a result, there is a vast array of treatments that are marketed to those with ADHD and their families. However, the evidence behind such treatments is variable, with some approaches being studied or recommended more than others. This makes it challenging for parents and clinicians to identify which treatments have research evidence supporting their effectiveness. In an effort to educate our clients and their families about the most effective treatments and interventions for ADHD in children and adolescents, the New York State Association of Neuropsychology (NYSAN) has created this resource, which reviews evidence for a wide range of treatments. Please feel free to share the information with colleagues and clients.

Note that this document is intended only to summarize available treatments and the research evidence behind them and does not reflect NYSAN's support of any one treatment.

ADHD and Its Treatments

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What is ADHD?

ADHD is characterized by pervasive behavioral patterns of inattention and/or impulsivity/hyperactivity that are developmentally inappropriate in their frequency and severity,¹ and which result in significant impairment.² While ADHD is the most commonly diagnosed childhood psychiatric disorder, its prevalence rates vary based on the population studied, with many epidemiological studies reporting 9% of boys and 3% of girls meeting criteria for ADHD.³

There are three primary presentations of ADHD described in the Diagnostic and Statistical Manual of Mental Disorders - 5th Edition (DSM-5). The predominantly Hyperactive/Impulsive Presentation (ADHD-HI) requires the presence of six of nine hyperactive and/or impulsive symptoms, such as being overly active and always on the go, having difficulty waiting one's turn, frequently interrupting and intruding onto others, talking excessively or being unable to play or engage in tasks quietly. The predominantly Inattentive Presentation (ADHD-I) requires the presence of six of nine symptoms of inattention and/or disorganization. Children with ADHD-I are often easily distracted, struggle to sustain attention and focus, have difficulty engaging in tasks requiring sustained mental effort, and may be forgetful and have difficulties planning and organizing tasks and activities. The combined presentation (ADHD-C) requires the presence of six of nine symptoms of inattention, as well as six of nine symptoms of hyperactivity/impulsivity. In addition for each presentation, the symptoms must occur in at least two settings (e.g., home and school) and must have been present prior to the age of twelve.

In addition to the behavioral symptoms of ADHD, many children with the disorder also demonstrate weaknesses in underlying cognitive skills more commonly known as executive functioning skills, such as working memory, response inhibition, organization, and various academic abilities.^{4,5} Therefore, the development of treatments targeting ADHD have focused not only on improving the core symptoms of inattention, hyperactivity and impulsivity, but on addressing these cognitive skills as well. This has resulted in a very wide range of treatment options, which can be overwhelming and confusing to families attempting to identify what will be most helpful for their child or adolescent.

How is ADHD Diagnosed?

There is currently no single test or approach that can be used to determine an ADHD diagnosis. The DSM-5 diagnostic criteria for ADHD is largely behavioral and symptom based which leads to diagnostic challenges, as symptoms associated with ADHD are not unique to the disorder. Difficulties with concentration and self-control are observed in ADHD, as well as in a variety of other disorders including depression, anxiety, and autism.^{1,6} As a result, alternative explanations for the symptoms must be considered. Furthermore, many children with ADHD may have another (i.e., comorbid) disorder, such as a learning disability, an anxiety disorder, and/or Oppositional Defiant Disorder. The impact of these co-occurring disorders must be teased apart from the symptoms of ADHD. Finally, the presence of symptoms alone is not enough to meet DSM-5 diagnostic criteria for ADHD. There must be clear evidence that the symptoms impair social, academic, and/or work functioning relative to peers. Therefore, the diagnostic approach recommended by most experts includes a comprehensive clinical interview with parents, a separate interview with the child/adolescent, and collateral reports including rating scales completed by

parents and teachers. Psychometric testing also is recommended when learning issues are suspected. Furthermore, when additional information is needed to reach clarity on the diagnosis, direct observation of the child, interviews with the teachers, and/or review of school records including teacher comments on report cards may be warranted.^{7,8,9} A diagnosis of ADHD is generally made by a clinical psychologist, clinical neuropsychologist, or physician.

What are the current treatments for ADHD?

There is general consensus that only ADHD treatments and interventions proven effective should be recommended by psychologists and physicians. These approaches are termed “evidence based” because there is research data to support their effectiveness.⁹ However, not all research is equal. Studies must be methodologically robust and findings need to be replicated, before conclusions about effectiveness can be made. Randomized, blinded, placebo control studies, ones that have a treatment and placebo group, and where neither subjects nor researchers are aware of group status, are the gold standard. However, this approach is not always feasible. The American Psychological Association (APA) recommends that conclusions about treatment effectiveness should be based on multiple factors which include systematic reviews, reasonable effect sizes, clinical, not just statistical significance, as well as a body of evidence supporting the intervention.¹⁰

Pharmacological Interventions

Medication is the best-supported treatment for ADHD and is recommended as a first line treatment for children and adolescents by the American Academy of Pediatrics.⁹ For children under six years of age, stimulant medication (specifically methylphenidate) is recommended should symptoms continue to have a significant effect on functioning after evidence-based behavioral interventions are attempted⁹. Although, medication helps most children (about 70-75%) improve concentration and reduce hyperactivity and impulsivity, medications do not “cure” ADHD, in that symptoms return when the medication is discontinued.¹¹ Furthermore, ADHD medication does not correct underlying cognitive difficulties, organizational difficulties, or academic problems; however, it may make individuals more available to learn skills and behavioral strategies.^{12,13,14,15} Consequently, medication intervention often is most effective when paired with behavioral interventions and skill development.¹⁵

Medications for ADHD are generally considered safe, even for long-term use.¹¹ However, different medications have differing side effects. It may take time to find the most effective medication and dosage to control ADHD symptoms while minimizing side-effects. The most common side effects are reduced appetite, trouble sleeping, headaches, stomach aches, irritability, and increased heart rate.^{16,17}

Medication interventions in children under six years of age have been studied less than in older children. Nevertheless, there is evidence that side-effects may be more problematic in younger children.^{18,16} Whatever the age of the child, medication interventions should include close collaboration with the prescribing medical professional with expertise in ADHD—usually a pediatric neurologist, psychiatrist, pediatrician, or nurse practitioner (psychologists do not prescribe medication in NY State)—and parents, as well as teachers. This ensures optimal communication and the greatest likelihood of identifying the most appropriate medication and

dosage, managing side-effects, and discontinuing ineffective medications. Maintenance of medication may be managed, thereafter by the primary care physician with periodic follow-up with the ADHD expert.^{18,19}

Other, non-stimulant medications also exist to treat ADHD. The choice to use stimulants or non-stimulants ultimately is the decision of the prescribing medical professional in collaboration with a child's parent.

Stimulants. Stimulant medications quickly impact behavior after they are ingested (i.e., within 30-45 minutes) and are effective for approximately four to 12 hours. Afterwards, ADHD behaviors return to their pretreatment levels. Stimulant medications include: 1) methylphenidate (and ^adexmethylphenidate) with the brand names of: Ritalin, Ritalin SR, Ritalin LA, Concerta, Daytrana Patch, Metadate CD, Metadate ER, Methylin, Methylin ER, Quillivant XR, Focalin^a, and Focalin XR^a, and 2) amphetamines (^bmixed amphetamine salts, ^cdextroamphetamine, ^dlisdexamfetamine) with the brand names of: Adderall^b, Adderall XR^b, Dexedrine^c, Dexedrine Spansules^c, and Vyvanse^d. Stimulants can be short-acting (4-6 hours) or long-acting (8-12 hours). The suffix designations of ER, XR, CD, LA, and SR indicate longer acting forms. Research has not consistently supported the superiority of any one of these medications; however, stimulants generally have been found to be more effective than non-stimulants.^{20,21,22,23} Additionally, effectiveness may vary from one individual to another.^{20,9}

Non-stimulants. Non-stimulant medications take longer to become effective (sometimes up to 6 weeks). They are also metabolized slower and require gradual build up to an optimal dose and tapering down prior to being discontinued. One advantage of non-stimulant medications over stimulant medications is that they yield a more stable effect. ADHD behaviors do not return to pretreatment levels after four to 12 hours because these medications do not quickly wear off.¹⁶

The most researched non-stimulant is atomoxetine (brand name Strattera), which is supported by some research as being as efficacious as methylphenidate.²⁴ It often is prescribed when stimulants are not effective or not well tolerated. Individuals taking atomoxetine require monitoring for agitation, irritability, suicidal thinking, and self-injurious behavior. The most common side effects for atomoxetine are gastrointestinal issues such as change in appetite, abdominal pain, and vomiting.¹⁶ Other approved but less researched non-stimulants used to treat ADHD include guanfacine ER (brand name Intuniv) and clonidine hydrochloride (brand name Kapvay).²⁵ These medications sometimes are prescribed in combination with a stimulant to manage ADHD symptoms. Other non-stimulant medications with efficacy in moderating ADHD behaviors include: propranolol (Inderal), bupropion (Wellbutrin), modafinil (Provigil or Nuvigil), tricyclic antidepressants such as desipramine (Norpramin) and imipramine (Tofranil).

Stimulant medications generally are considered first line treatments for ADHD symptoms. However, other comorbid conditions (e.g., tics, Tourette's syndrome, anxiety disorder, seizures, and substance abuse) may influence the choice of prescribed medication and/or other treatment.²⁵ Concerns about the possible misuse of medications (referred to as the "diversion of medication") may also influence the choice, as some medications must be absorbed through the digestive system and are less likely to be abused.⁹

Behavioral Interventions

Parent Training. Parenting a child with inattentive, hyperactive and/or impulsive behaviors is often challenging and can lead to negative parent-child interactions and the development of maladaptive and counterproductive parenting strategies for managing ADHD behaviors.²⁶ Integral to the treatment of ADHD is modifying parenting behaviors to increase positive outcomes between parents and their children and to decrease parenting stress.²⁷ This is particularly important since poor parenting practices have been found to be one of the most robust predictors of negative long-term outcomes in children with behavior problems.²⁸ Behavioral Parent Training (BPT) is one of the most empirically supported psychosocial treatments for ADHD.²⁹ Multiple studies have documented the impact of BPT in improving child behavior,^{30,31} improving maladaptive parenting behavior, and even reducing parenting stress.³² However, one caveat is that much variability exists in how parent training is delivered. Consistent adherence and fidelity to the manualized treatment has been shown to have a positive influence on outcomes. BPT can be delivered in large community groups, small clinic-based groups, and individual formats. Advantages associated with individualized versus group BPT include increased flexibility in terms of pace, content, the ability to provide individual attention to idiosyncratic problems, and potentially more active involvement by the parent, particularly for economically disadvantaged families.³³ There also is evidence that enhancements can be made to the BPT to increase attendance and engagement, particularly for parents at-risk of poor outcomes, such as single mothers who have limited psychosocial support.³⁴ Common components of BPT include the discussion/implementation of principles of positive reinforcement, parent-child relationship building, effective limit setting/punishment, problem solving, anger management, psychoeducation, homework and review, role playing/behavioral rehearsal, modeling, provision of materials, and review of goals/progress.²⁹

Evidence-based BPT is known to be particularly useful at younger developmental ages, and is encouraged as the first line of treatment for children aged six years and younger.^{35, 9} Notably, despite its known positive impact on child behavior, non-child factors, such as socioeconomic status and maternal mental health, are strong predictors of the efficacy of BPT on child externalizing behavior problems.³¹ Therefore, researchers are emphasizing the importance of combining evidence based treatment for adult mental health along with evidence-based parent training in an effort to further improve outcomes.³⁶

Classroom Management. Research suggests that in a classroom of 30 students, two to three children likely have ADHD.³⁷ Classroom management is a well-established intervention for youth with ADHD.⁹ It uses contingency management, which is a behavioral therapy approach that selectively rewards target behaviors. For example, token economies may be used to reinforce desired behaviors. The child earns tokens that later may be exchanged for desired “rewards.” Classroom management strategies have been shown to lead to improvements in teacher-rated ADHD symptoms and teacher-rated social skill measures in addition to increased daily work productivity.³⁸ Classroom interventions reduce off-task and disruptive classroom behavior in children with symptoms of ADHD with largest effects for consequence-based and self-regulation interventions.³⁸ Furthermore, interventions that are based on an analysis of the function of an individual child’s behavior (function-based interventions) have been proven to be more effective than non-function based interventions.³⁹ The impact of classroom interventions on symptoms of ADHD were seen mostly in general education classrooms than in other classroom settings (e.g.,

special education classrooms), where ADHD symptoms are more severe. However, students with and without ADHD were observed to reap the benefit of classroom-wide intervention strategies.³⁸

Targeted teacher training has also been offered as a means to better support students with ADHD and to help improve their functioning in the classroom. The aim of the training interventions are to help teachers meet educational needs by training them on more effective skills to manage children's ADHD behaviors in the classroom using positive reinforcement techniques, scaffolding of behaviors, and clear and natural consequences.

In addition, classroom adaptations, including preferential seating, modified work assignments, and test modifications, as well as tailored behavior plans and daily report cards can be provided through the implementation of a Section 504 Plan of the Rehabilitation Act of 1973 or a special education Individualized Education Program (IEP) as part of the Individuals with Disability Education Act (IDEA) to support school-age children with ADHD.⁴⁰ While such classroom accommodations are commonly utilized, the effectiveness of many if these accommodations have not been thoroughly studied and the studies that have been conducted have yielded inconsistent findings with regard to their effectiveness and whether they provide a differential boost to students with disabilities and ADHD.^{41,42,38,43,44}

Peer Interventions. Peer interventions are directed at improving social functioning for youths with ADHD. Traditional office-based social skills training alone has not been found to produce long-term positive effects.^{45,46} Since many children in these studies also were being treated with ADHD medication, the magnitude of behavior change from psychopharmacological intervention versus social skills training remains unclear. Although social skills training alone may not improve interpersonal functioning in children with ADHD, combining it with behavioral parent training increased parental engagement.²⁹ Other peer interventions delivered in recreational settings, such as Summer Treatment Programs (STP; including social skills training, coached group play with contingency management, home rewards aimed at social functioning), were proven effective.⁴⁷ Results were comparable to those from medication. These therapeutic summer camp experiences typically last for eight-weeks and employ intensive behavioral interventions administered by trained counselors. It is important to note that research participants who received behavioral classroom management and behavioral peer interventions (as part of the efficacy studies summarized above) were often concurrently receiving BPT. The literature notes it is difficult to disentangle incremental benefits from simultaneous treatments.

Other Treatments. Non-behavioral psychotherapeutic or cognitive behavioral treatments (i.e., individual therapy, play therapy, or cognitive therapy) have not been found to be clinically effective for youths with ADHD.²⁷ Although a problem-solving communication training group was minimally studied, there was initial evidence of a similar outcome in comparison to BPT when it was combined with intensive, multicomponent behavioral treatment.^{48,47}

Computerized Interventions

Multiple computerized programs claim to target ADHD specific symptoms, improving attention and working memory in addition to behavior and academic achievement. As these interventions

do not involve medication, they have become popular. However, they can be expensive and time consuming. Furthermore, the evidence to support their efficacy is limited.^{49,50,51}

Cogmed. Cogmed working memory training program may be the most widely studied program. While many of the original studies were performed by the developer, more recently independent studies were completed with inconsistent results. A recent and comprehensive review recommended that Cogmed be defined as a “Possibly Efficacious” Treatment for Youth with ADHD.⁵² Many studies note improvement on the trained tasks, but transferring these gains to daily activities has not been reliably demonstrated.⁵³ Additional reviews noted that claims about academic, behavioral, and cognitive benefits of these training programs remain unsupported in ADHD research.⁵⁴ In addition, other studies failed to demonstrate improvement in non-trained working memory tasks in children with more severe ADHD and learning disorders. Additionally, it is unclear whether the gains reported in some studies last.⁵³

Interactive Metronome. Interactive Metronome is another popular treatment for children with ADHD. The theoretical basis for Interactive Metronome is that motor planning and organizing are based on an internal sense of rhythm. Thus, interventions aimed at improving timing and rhythm could improve symptoms of ADHD. Unfortunately, only a few peer-reviewed studies have examined the impact of this intervention on ADHD symptoms and these were marred by poor methodological designs. Consequently, there is insufficient support for Interactive Metronome.^{55,9}

Brain Beat. Brain Beat is based on a similar premise as Interactive Metronome treatment. While the company reports several studies on its website, no published studies were identified to date.

Brain Gym. Brain Gym incorporates kinesthetic movements to promote neurological re-patterning. This approach was not supported by several research studies in peer reviewed journals. Additionally, considering the weak scientific support for the theories upon which Brain Gym is based, the American Academy of Pediatrics in 1999 cautioned against its use (also see ^{56,57}).

Fast ForWord and Earobics. These interventions were originally designed for treating language-based difficulties.⁵⁸ There is no evidence from research with strong methodological designs for their efficacy for the treatment of symptoms of ADHD.⁵⁷

Executive Function Interventions

Executive functions (EF) are higher order thinking skills that allow individuals to regulate and orient their behavior to reach a goal. These skills include inhibitory control, self-regulation, cognitive flexibility, and working memory, as well as planning and organizing. EF interventions were developed in accordance with the clinical model of psychopathology, which contends that the most effective interventions work to improve underlying neurobiological substrates and core psychological/cognitive features. This premise also is supported by a body of literature showing that neurodevelopmental processes are responsive to environmental influences. EF interventions, therefore, target ADHD-related executive function weaknesses observed.

Facilitative Intervention Training (FIT). FIT programs were first proposed in the early 2000’s to improve executive functioning. They differ from the other non-pharmacological treatment

approaches by trying to promote the development of attention and executive functioning rather than compensate for weaknesses in these functions. The underlying premise of FIT programs is that extensive training (involving repetition, practice, and feedback) can lead to enduring and measurable improvements in the development and efficiency of executive functions. These improvements, in turn, are thought to generalize to abilities and activities that are mediated by the same neural circuits.

Studies that investigated this intervention generally targeted short-term and working memory, attention, set-shifting, and a mix of executive function skills (e.g., inhibition and short-term memory). Recent studies mostly employed computerized-based interventions. Of those, several used Cogmed Working Memory Training (see above). Other recent studies included “intrinsically rewarding” (i.e., fun) tasks. For example, TEAMS (viz., Training Executive, Attention, and Motor Skills) uses games and physical exercises involving sequencing, following directions and rules, and planning, applied within a social context to gradually increase neurocognitive and motor skill in preschool children.⁵⁹ A significant decline in ADHD symptom ratings by parents and teachers followed treatment. Furthermore, this clinical improvement was maintained three months following termination of active treatment. Children who used the game version of working memory training programs showed greater motivation (i.e., spent more time training), better performance (i.e., more sequences reproduced and fewer errors), and superior abilities at post-training than children who participated in regular working memory training.

The question of whether maturation and/or efficiency of neural circuitry underlying targeted EF can be accelerated with FIT programs (via protracted training, practice, and feedback) cannot yet be answered. FIT programs that targeted short-term memory yielded gains in children’s cognitive performance that remained evident at three-to-six months. However, programs that targeted mixed EF (such as combined inhibition and short term memory), set-shifting, or only attention processes did not produce significant improvements in the trained cognitive domains.⁵⁰ Furthermore, it should be noted that training short-term memory was not associated with significant improvements on non-trained tasks. There also were minimal-to-no-objectively measured improvements in behavior, academics, and cognitive functioning.

Organizational Skills Training. Organizational and planning skills are often impaired in children with ADHD. These deficits result in children struggling to keep track of their belongings, assignments, and allotment of time in planning activities. A recently developed Organizational Skills Training program (OST) may be effective in mitigating these behaviors.⁶⁰ The program trains elementary age children, along with their parents and teachers, to develop tools and routines for tracking assignments, managing belongings, and allocating time for planning tasks. Parents and teachers receive guidance in behavior modification, whereas children are provided with instruction and practice from clinicians in individual sessions. OST was shown to improve organizational skills in children with ADHD, with beneficial effects lasting into the next school year (evidenced in homework compliance, behavioral management, academic productivity, and familial tranquility).^{60,61}

Several other interventions were also found to improve organizational skills. Parents and Teachers Helping Kids Organize (PATHKO) is one of those. PATHKO trains parents and teachers to develop individualized goals that they can prompt and reward. However, unlike the OST program,

the PATHKO intervention does not provide children with specific skill instruction. Whereas each program utilizes praise and rewards, PATHKO additionally allows for response cost, such as removal of privileges following an undesirable behavior. Improvements in organizational skills obtained with PATHKO also remained positive at follow-up at one month post treatment, as well as the following school year.⁶⁰

Homework, Organization and Planning Skills. Homework, Organization and Planning Skills (HOPS) is a program that was utilized in schools for training children with ADHD and their parents. Individualized intervention is provided to children by school-based mental health providers for 11 weeks, targeting specific skills in material management, homework tracking, and time management. Self-monitoring and skill maintenance also are included, as is a reward system. Currently there is minimal available peer-reviewed literature on this specific program. However, in one randomized trial, improvements in organizational skills continued to be observed at three months, but teacher ratings did not identify group differences with regard to waitlist controls.^{61,62}

A quantitative meta-analysis evaluated a variety of organizational skills training programs in children and adolescents including the OST program and HOPS, the Child Life and Attention Skills (CLAS), Family-School Success (FSS), and Supporting Teens' Autonomy Daily (STAND). The analyses suggested that organizational skills programs were most effective at increasing parent-rated improvements in organizational skills, with large effect sizes observed. Teacher-rated improvements in organizational skills resulted in more moderate effects. Improvements on parent and teacher-rated symptoms of inattention and academic enhancement were small.⁶¹

The interventions in this section all use strategies that help teach the child and/or parent specific concrete strategies and skills associated with executive functioning such as; organization, planning, working memory, and self-regulation. Each of the above programs are administered in a standardized format that utilizes repetition and practice. The most successful programs incorporate strategies that are directly applicable to life skills. For example, teaching a child how to monitor his homework and plan out long-term assignments. On the other hand, more research is needed for portions of programs that teach strategies for cognitive skills such as short-term memory, as the improvements have not been empirically demonstrated to transfer to real life settings. Overall there are many reasons executive programs are appealing to children and their families. For one, they tend to be a cost effective option when compared with individual or family psychotherapy because they can typically be administered in a group format and the treatments can be administered by trained ADHD coaches or individuals who do not have a specialized or doctoral degree.

Diets, Vitamins, and Nutritional Supplements

Although there is inconsistent evidence that use of special diets and nutritional supplements can resolve ADHD symptoms, well-balanced and healthy diets are known to yield beneficial health effects that can positively impact attention, concentration, and behavior.⁹ In contrast to the "Western-style" diet, a balanced diet that is low in fat and refined sugars and emphasizes fiber, folate, and omega-3 fatty acids is encouraged.⁶³

Other dietary strategies can be influenced by genetic, allergic and/or geographical history. For example, low zinc levels could be a concern for children who have relocated from regions where this tends to be endemic and can be addressed in consultation with their health care provider. Overall however, many dietary interventions listed below are difficult to implement and may not be suitable for extended use, particularly given the already known demands and stressors faced by parents with children with inattention, impulsivity, and oppositional behaviors.

Sugar/Aspartame Restricted. Sugar increasing hyperactive and inattentive symptoms is a commonly held belief among many.^{64,65} However, various studies and meta-analyses have consistently failed to support this notion and at this time there is no evidence that sugar intake increases symptoms of ADHD.^{66,63,64,65}

Fatty Acid Nutritional Supplements. Studies of the effects of supplementation with fatty acids on symptoms of ADHD have been highly inconsistent, with some studies demonstrating small effects, while others found no benefit.^{67,68} Overall, recent meta-analyses, as well as a Cochrane review concluded that there is little evidence that fatty acid supplementation provides benefit for ADHD symptomatology, although there was some limited evidence that using a combination of Omega 3 and Omega 6 may have greater benefit.^{69,70} However, it should be noted that some children with ADHD may have genetically based impairments in fatty acid metabolism and lower levels of long chain polyunsaturated fatty acids.⁶³

Iron Deficiency. Studies exploring the effect of iron deficiency in children with ADHD have not reported consistent findings.⁷¹ While the effect of iron supplementation on ADHD symptoms has not been shown to be significant, there may be a low threshold effect when iron levels are particularly low (e.g., 7 ng/mL).⁶³ Specifically, serum ferritin levels may be related to the amount of medication needed to improve ADHD symptoms.⁷² Thus, study of iron levels as potential predictors of medication responses was felt to be warranted.⁶³

Zinc Deficiency. Zinc has been described as an important cofactor for metabolizing dopamine, a neurotransmitter believed to be involved in ADHD.⁷³ However, the literature associating zinc deficiency with hyperactive-impulsive behavior remains unclear and researchers have found that zinc deficiency has only a marginal prevalence rate amongst those diagnosed with ADHD, particularly in US samples.⁷⁴ However, some studies have reported enhanced benefit from d-amphetamine, when it was supplemented with zinc.^{75,74} Variability in the reliability of the diagnostic procedures used to assess the benefits of zinc supplementation and limited sample representativeness, with the largest population sampled coming from areas with suspected endemic zinc deficiency, tend to underscore and limit the generalizability of the research in this area.⁷⁶ Consequently, the prospect of employing zinc as a treatment for U.S. raised children with ADHD is cautioned, particularly given the high zinc doses were described as above the recommended upper tolerable limit and which at high doses can be toxic or at least cause gastrointestinal side effects.⁷⁶

Feingold Diet. The contribution of artificial food colors and other food additives (AFCA) to ADHD symptoms, particularly hyperactivity, has received significant consideration and review over the years.^{77,78,79} Approximately 30 years ago, Ben Feingold proposed a diet for children with sensitivities to food antigens or allergens and to dyes and coined it the “Feingold Diet.” The diet

specifies avoidance of foods and drinks containing artificial flavors and food coloring agents. Orange and red synthetic dyes, as well as preservatives, are particularly targeted for avoidance.⁶³ However, follow-up studies reviewing the efficacious treatment of diet modification on hyperactivity and attention have yielded inconsistent conclusions.^{77,79} Suggestions have been made that more precise mechanisms (e.g. electroencephalography and measurement of physiologic parameters) could be implemented to help narrow the subgroup of responders to such intensive restrictions. Notably, the restrictiveness of an AFC-free diet requires a significant level of food preparation and planning, which can burden and further stress the family of a child with ADHD. It also poses potential social-interaction limitations on the child diagnosed with hyperactivity, who is already at risk for poor psychosocial outcomes. Direct nutritional education for parents and children on healthy dietary patterns and options for ideas on how to better balance nutrition is suggested as a potential promising and practical complementary alternative treatment of ADHD.

Food Coloring. About eight percent of children exhibit a reaction to food coloring. Although studies demonstrated behavioral improvement in children by eliminating food coloring from their diets, the effect was small. Additionally, it was only observed with non-FDA approved food dyes. Thus, this benefit was observed mostly for children residing outside the United States.⁸⁰

Oligoantigenic (“Elimination Diet”). The Elimination Diet involves removing known food antigens and/or allergens and providing hypoallergenic food alternatives. This can include removal of cow’s milk, cheese, wheat cereals, egg, chocolate, nuts, and citrus fruits. Skin tests for allergic reactivity can be unreliable and elimination diets are now suggested to test for specific food intolerances.⁶³ The process of identifying the offending item with elimination diets is complex and time consuming; requiring a two-to-three week period of restricted elimination with restricted foods introduced each week in “food challenges”, one at a time to assess an allergic response in the form of an escalation of behavioral and cognitive symptoms, until the offending item or items are identified. Many studies have shown improvement in ADHD symptoms in children with food sensitivities.^{81,82} A recent randomized controlled study further demonstrated significant benefit of the elimination diet in a general group of children with ADHD, with return of symptoms upon food challenge.⁸³ Notably, parents were not blinded to the treatment type in this study, although pediatrician ratings of ADHD symptoms were properly blinded. Additionally, a recent meta-analysis also demonstrated large effect sizes for the few foods elimination diet.⁸⁴ Thus, it appears that elimination diets may provide some benefit. However, strict elimination diets are also burdensome and often impossible to maintain long-term. At this time, the role of the elimination diet in the treatment of ADHD remains uncertain.

Ketogenic Diet. This is a low carbohydrate and high fat diet that was developed in the 1920’s to treat epilepsy.⁶³ High comorbidity between epilepsy and ADHD suggests these disorders may benefit from the same treatments. Nevertheless, the literature does not support the notion of the ketogenic diet having value in treating ADHD.

Herbal and Nutritional Products. Although widely discussed in the popular health media, current research does not support any substantial impact on ADHD symptoms from the use of herbal and nutritional products such as St. John’s Wort or Ginkgo biloba.⁸⁵

Neurofeedback

Neurofeedback is a computer-aided technique that is based on principles of classical conditioning and learning theory. It trains individuals to self-regulate brain activity in order to achieve a calmer state, thereby lessening ADHD symptoms.⁸⁶ Given its noninvasive nature, neurofeedback has become a treatment of much interest. Two major paradigms exist, with one training theta/beta waves, while the second trains slow cortical potentials.⁸⁷ While many studies have evaluated the effectiveness of neurofeedback, multiple methodological issues have been identified which need to be kept in mind when evaluating the evidence.

One of the major questions has surrounded appropriate control groups, blinding of raters and identifying whether effects of neurofeedback are specific to training of brain waves or are due to the learning of more general self-regulation strategies.⁸⁶ Research on neurofeedback has been inconsistent. Multiple studies have shown neurofeedback to be effective in reducing symptoms of ADHD,^{86,87} with several studies demonstrating neurofeedback to be as effective as medication.^{88,89} However, most studies that have demonstrated the effect of neurofeedback did not have proper control groups or were not blinded. Effect sizes were far lower and did not reach statistical significance for probably blinded reporters, such as teachers.⁵¹ The most recently published meta-analysis of randomized controlled studies noted that while significant effects were found for ADHD symptoms when raters were unblinded (e.g., parents), this effect was not significant when blinded raters were used or when studies included active or sham controls (e.g., medication or non-brain related feedback). Furthermore, no effects were seen on laboratory measures of inhibition or attention.⁹⁰ Thus, at this point, while neurofeedback has shown some promise as a potential treatment for ADHD, evidence from well controlled studies does not provide enough support and more research is needed.

Exercise and Mindfulness

Exercise. Exercise has been demonstrated to benefit the cognitive functioning of children (e.g., enhancing mental flexibility).^{91,92,93} Some research found small benefits for short, acute movements.⁹⁴ Nevertheless, more recent studies suggest that vigorous exercise may facilitate executive functioning in children with ADHD, particularly inhibition, planning, and working memory.⁹⁵

The proposed mechanism for the benefit of exercise on cognitive functioning is based on the theory that it causes dopamine release. Dopamine is a brain activating neurotransmitter, which has been implicated in ADHD.⁹⁶ Thus, increased dopamine would be expected to heighten brain activation to potentially improve cognitive focus and, in particular, executive functioning ability.^{97,98,99}

Although additional research is necessary, evidence is increasing that exercise positively affects the cognitive functioning of children with ADHD.^{100,95}

Mindfulness. Mindfulness is enhanced awareness of one's internal and environmental contexts. Exercises to develop mindfulness include teaching children to consider new ideas, exercise cognitive flexibility, and meditation. Although literature on the effectiveness of mindfulness training in children with ADHD is not conclusive, some positive preliminary findings have been observed. For example, improvements were reported for self-regulatory skills and for behavioral

compliance in children presenting with ADHD symptoms.^{101,102} Similarly, adolescents exhibiting ADHD symptoms showed improvements on self-reported externalizing and internalizing symptoms, as well as on attention and executive functioning tasks. However, the improvements appeared to diminish with time.¹⁰³ A recent meta-analysis demonstrated that mindfulness-based training in children produced small improvements on self- and observer-reports of inattentive and hyperactive/impulsive symptoms of ADHD in children.¹⁰⁴ Despite some promising improvements, the heterogeneity between studies was identified as problematic, bringing the importance of these significant findings into question, as some of the results were thought to be a result of variation in self-report and age of participants. The authors advocated for more research in regard to the type of mindfulness intervention (e.g., mindfulness as part of Dialectical Behavioral Therapy, mindfulness in isolation, mindfulness in conjunction with yoga) and a wider variety of methods to evaluate children's functional outcomes.

Combination Treatments

Research on the efficacy and outcome of combination treatments such as medication in addition to behavioral interventions or psychotherapy varies. Some research supports the added potential benefits of combination treatments,^{105,106} while some did not find additional impact of these combined interventions.^{107,108}

The MTA Cooperative group¹⁰⁶ found that children receiving medication combined with intensive behavioral treatment incorporating the parents and school, fared better than those receiving only behavioral or community care. While statistically, the combined treatment group did not differ from the medication only group on measures of ADHD, the combined treatment participants showed improvements on measures of behavioral and psychological functioning that often coincide with ADHD including: oppositionality, internalizing symptoms, teacher-rated social skills, parent-child relations, and reading scores. Therefore, the researchers argued that medication in addition to deliberate organizational skills training and behavior strategies are more effective than either treatment in isolation in treating the whole child. At a 24-month follow up, however, there were no added benefits for combination treatment over medication management on symptoms of ADHD.¹⁵

In order to better understand the interaction between treatments on a child's outcome, Pelham et al.,¹⁰⁵ examined the effects of treatment order for medication and behavioral interventions. Children were randomly assigned to receive medication first or behavioral intervention first. If they continued to demonstrate clinical impairment after eight weeks, then they were provided with the other intervention (medication treatment for behavioral intervention first group and behavioral treatment for the medication first group). Pelham et al.,¹⁰⁵ found that children who received behavioral intervention first, were significantly more successful at improving classroom behavior and decreasing teacher and parent ratings of symptoms of Oppositional Defiant Disorder (ODD), and disciplinary actions than the medication first group. The authors attributed some of this success to the higher parent engagement in the behavioral intervention when it was provided as a first treatment.

However, similar to Hechtman et al.,¹⁰⁷ and the MTA group, a higher proportion of children who received medication first did not require further treatment whereas a higher proportion of children

who received the behavioral intervention first went on to then be treated with medication. On the other hand, for those children who required both treatments (i.e. the first treatment was not enough to provide significant reduction in symptoms), children who received medication treatment first were far more likely to be using medication at the study's conclusion than those who received behavior management first. Overall, the results imply that for children who exhibit significant ADHD symptomatology who likely need combined treatment, beginning with behavioral interventions is the recommended course as it was found to be more beneficial for not only child outcome but parent engagement.¹⁰⁵

Hechtman et al.,¹⁰⁷ also studied the implications of using combination treatment over the course of two years. These authors screened participants so that only children with ADHD were included, and those with other commonly comorbid disorders were excluded (e.g. Learning Disorders, and Conduct Disorder). Children were assigned to one of three groups including medication only; medication plus academic remediation, organizational skills training, and psychotherapy; and medication plus therapy specifically designed to help children regulate their attention. On measures of parent rating of homework problems, and self-ratings of depression and self-esteem, there appeared to be no added gains for either of the combination treatments when compared to medication alone. However, significant improvements were indicated for all treatment groups.

Overall, additional research is needed on the efficacy of combination treatments and the differences in outcome highlight the diversity of presentations between children with ADHD and the various implications for selecting treatment. It is difficult to compare the efficacy of the above studies as the participants and outcome variables are quite different from one another. The generalizability of findings is also limited by the sample selection criteria. For example, the research by Pelham et al.,¹⁰⁵ included children who may have experienced comorbid challenges in learning and/or behavior, children in Hechtman et al.,¹⁰⁷ had fewer comorbidities. The research was consistent in determining that symptoms specific to ADHD itself may not have been improved by combination treatments in comparison to medication alone. However, behavioral or psychosocial interventions in conjunction with medication may be more successful at treating children with ADHD who also experience difficulties with learning or oppositionality.¹² As such, children with learning difficulties, oppositionality or poor academic performance as a result of disorganization in addition to their ADHD symptoms may benefit from added treatment components, similar to the children in the MTA group¹⁰⁶ and Pelham et al.,¹⁰⁵ studies. On the other hand, children who do not experience these symptoms may not have the same level of added benefit from psychotherapy or skills training programs.

Summary

This review of research was designed to examine the strength of empirical support for common treatments of ADHD. Overall, many of the treatments had at least some empirical support. However, empirical support that was replicable and that utilized randomized controlled trials was available for only some of the interventions.

Pharmacological interventions, for example, have the most empirical support, and are considered the first line of treatment for children and adolescents aged six and older. For younger children, research widely supported medication secondary to behavioral interventions.⁹ Behavioral

treatments are also extremely popular choices for many families in treating children or adolescents with ADHD. The most successful behavioral treatments often include the whole family.¹⁸ Classroom management techniques, as well as peer interventions are also available; however, in isolation, these interventions are less impactful than parent management training, or behavioral interventions in conjunction with medication. In fact, behavioral strategies as a whole are often thought of as most helpful when provided in conjunction with medication management.^{15,106} Other interventions, particularly working memory training, neurofeedback and nutritional supplementation, have shown far less effect with far more inconsistent findings across studies. While certain dietary interventions can be effective for some children, their implementation is tedious and thus often difficult. Exercise and mindfulness interventions are beginning to be studied more and while they show promise, more support is needed. The best options, determined in consultation with a health care provider, ultimately depend upon consideration of symptom severity and of family preferences.

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