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## Restriction and Elimination Diets in ADHD Treatment

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The numerous “alternative” or “nonmedical” treatments that have been proposed for attention deficit and hyperactivity disorder (ADHD) over the years include several kinds of dietary interventions, including single nutrient supplements,<sup>1</sup> multivitamin supplements,<sup>2,3</sup> supplementation with omega-3 fatty acids,<sup>4–7</sup> and others. Among the most enduring ideas has been the use of a food restriction or food elimination diet, hereafter referred to simply as an elimination diet.

### ELIMINATION DIETS AND HEALTH

The concept of an elimination diet to improve health was first proposed by Albert Rowe<sup>8</sup> in 1926 in regards to food allergies and spelled out in his subsequent book. The concept of “Allergy of the Nervous System” dates back to 1934, when Lapage<sup>9</sup> mentions the use of Rowe’s elimination diet. Subsequently, hundreds of papers have been written on the general topic area of allergy, food, and the nervous system. In 1976, Hall<sup>10</sup> referenced the use of an elimination diet for the treatment of “behavioral disturbances including headaches, convulsions, learning disabilities, schizophrenia, and depression” related to allergy of the nervous system. It was around this same time that the Feingold diet was introduced as treatment of hyperkinetic syndrome, as detailed herein. Therefore, the idea of an elimination diet to help child or adult mood, attention, or behavior is not new, but has regained renewed interest in recent years.

The focus of elimination diets is to remove specific foods from the diet in an effort to eliminate potential allergens that occur naturally in food (eg, eggs, wheat, dairy, soy) or artificial ingredients that may have allergenic or even toxicant effects (eg, synthetic food additives: artificial colors, flavors, sweeteners, as well as flavor enhancers [like monosodium glutamate (MSG)] and preservatives). These diets are used to attempt to diagnose and treat food allergies and intolerances.

Food elimination diets vary in their specific content, but take 3 main forms. A single food exclusion diet excludes one suspected food, such as eggs. A multifoed exclusion diet, such as the 6-food elimination diet, eliminates the most common food allergens: cow-milk protein, soy, wheat, eggs, peanuts, and seafood. A “few foods diet” (also called an oligoantigenic diet) restricts a person’s diet to only a few less commonly consumed foods (eg, lamb/venison, quinoa/rice, pear, and others with low allergenic potential). The “few foods diet” must be overseen by a properly qualified professional (eg, dietitian) to avoid nutritional deficiency, but is effective at identifying multiple food allergies in an individual.<sup>11</sup> Much of the use of these diets in the medical literature is targeted at single specific food allergies (eg, cow’s milk<sup>12</sup> or physical symptoms thought to potentially be related to food allergies, such as esophagitis).<sup>13,14</sup>

Other specific elimination diets exist, such as a gluten-free diet and the Kaiser Per-manente (or Feingold) diet. The gluten-free diet is currently the only successful treatment for patients with celiac disease<sup>15</sup> and is also being used to treat nonceliac gluten sensitivity.<sup>16</sup> Gluten is the protein found in wheat, rye, and barley, and thus, any item in the diet containing these grains (including some food additives) must be removed. A gluten and casein-free diet is also being tested in autism.<sup>17</sup> The Feingold diet eliminates food colorings and sometimes certain preservatives and foods with naturally occurring salicylates.<sup>18</sup> The Feingold diet was later adapted to only exclude artificial colorings and preservatives, which Feingold came to think were the pertinent factors in ADHD. *No. Dr. Feingold said the dyes should be studied first because it was easier, not more important.*

always

All elimination diets use the same 2-step process, wherein the diet is followed for a period of time; then, if symptoms remit, foods (or food additives) are reintroduced one at a time to test for a return of symptoms. When using the “few foods diet,” this process is lengthy, because many foods must be tested until enough foods have been identified to reinstate a healthy balanced diet without allergens. When food allergy is suspected, skin prick allergy testing can accompany dietary treatment. More commonly, the dietary intervention is purely “empirical” in that foods are eliminated and reintroduced while symptoms are monitored.

Allergists define **food allergy** as an immunologic response in the body after exposure to a food item. Common manifestations of food allergy include skin responses (urticaria), sensitivity/swelling in the mouth, rhinitis, breathing difficulties, and gastrointestinal issues ranging from vomiting to diarrhea; less well-known neurologic symptoms, like headache, anxiety, confusion, nervousness, and lethargy, have also been reported.<sup>19</sup>

On the other hand, **food intolerance** is defined by allergists as a nonimmunological (ie, nonallergic) response to a food item, which may be due to enzyme deficiency (eg, lactose intolerance) or another nonimmunological hypersensitivity reaction such as to food additives.<sup>20</sup> Food intolerances can also cause gastrointestinal difficulties, but often also result in other symptoms, which can range from headache and blurred vision to mood changes, fatigue, and pain. Pelsser and colleagues<sup>21</sup> hypothesized that ADHD involves food hypersensitivity (intolerance). This type of food intolerance is often considered to be a toxicologic or pharmacologic response to chemicals found in food. However, intolerance is difficult to verify because the idea of intolerance proposes that reaction may occur after a

substantial time period; furthermore, the mechanisms of such intolerance are not necessarily demonstrated for most additives.

However, some examples have been compelling. A well-known example is tetrodo-toxin, which is a neurotoxin found in Fugu fish commonly consumed in Japan.<sup>22</sup> Another is the common food additive, MSG, which may have excitotoxic effects in the nervous system.<sup>23</sup>

To illustrate the latter effect, an excitotoxin elimination diet was tested in a group of fibromyalgia patients who also suffered from irritable bowel syndrome. Fibromyalgia is characterized by a constellation of neurologic symptoms including widespread muscle pain, cognitive dysfunction, headache, paresthesias, difficulty sleeping, balance issues, and fatigue. Those who improved on the diet (defined as >30% of their symptoms remitting) were challenged with MSG in a crossover placebo-controlled double-blind manner. A significant return of symptoms was seen with MSG as compared with placebo.<sup>24</sup> It is important to note that fibromyalgia patients tend to suffer from cognitive difficulties, including problems with attention.<sup>25</sup> This toxicologic response to MSG therefore may be of importance in ADHD, because, similar to fibromyalgia, disordered glutamatergic neurotransmission has also been implicated in ADHD.<sup>26–28</sup> At least one study has examined the effects of MSG in children with ADHD, although in combination with removal of other additives.<sup>29</sup> Furthermore, other research has demonstrated that **artificial food colors may act synergistically with MSG**,<sup>30</sup> a possibility yet to be examined in relation to ADHD.

## ADHD APPLICATIONS

As mentioned earlier, the specific hypothesis that synthetic food colorings influence ADHD (at that time, hyperkinetic reaction), via either allergenic or pharmacologic mechanisms, was introduced in the 1970s by Feingold.<sup>31–33</sup> Feingold was an allergist, so his predisposition was to evaluate for potential allergens in patients. He suggested initially that children who are allergic to aspirin (which contains salicylates) may be reactive to synthetic food colors as well as naturally occurring salicylates, although he later focused in particular on food color additives. He proposed a diet free of foods with a natural salicylate radical and all synthetic colors and flavors to treat hyperactivity. This diet is also referred to as the Kaiser Permanente diet. This approach is still promoted today by the organization he founded (<https://www.feingold.org/>). A narrower approach simply restricts synthetic food colors, although these are sometimes also restricted as part of more general diets.

(parents founded the Feingold Assn not Dr. Feingold)

This is an error

True until renamed by the media in 1980s

In the 1970s and 1980s, various versions of the Feingold diet were heavily studied in the United States, but more recently this type of diet has been investigated primarily in Europe. In 1982, the National Institutes of Health convened a consensus development conference on defined diets and childhood hyperactivity, which recommended further study.<sup>34</sup> In the subsequent 30 years, several major reviews have been attempted, albeit on a persistently weak literature. Those reviews are summarized in Table 1. Herein, their insights and a few others are briefly highlighted.

An initial meta-analysis in 1983<sup>35</sup> included 23 studies of varying quality regarding the efficacy of the Feingold diet; the authors concluded that the composite effect size ( $d = 0.11$ ) was too small to be important, setting the tone for 2 decades of professional skepticism as to

the value of elimination diets. More recently, however, in 2004, Schab and Trinh<sup>36</sup> reviewed 15 higher quality studies, which were all double-blind, placebo-controlled studies focused on food color elimination or challenge, plus 6 others for a supplemental analysis. They concluded that there was a reliable effect ( $d = 0.28$ ) linking synthetic colors to ADHD symptoms in parent ratings, but not in teacher or observer ratings. The effects seemed to be similar whether or not children were initially selected to be hyperactive. Although the results were equivocal (failure to see a reliable effect in teacher or observer ratings, least prone to hidden failure of study blinding), they spurred new interest.

About that same time, a widely publicized population-based study conducted in England<sup>37</sup> concluded that food additives contribute to hyperactivity, prompting the European Union Parliament recently to require warning labels on foods containing 6 colors (not all of which are approved for use in the United States by the US Food and Drug Administration, FDA<sup>38</sup>). The FDA has approved 9 synthetic colors for use in food subject to batch certification: FD&C Blue number 1 (brilliant blue), FD&C Blue number 2 (Indigotine), FD&C Green number 3 (Green S; fast green), Orange B, Citrus Red number 2 (Amaranth), FD&C Red number 3 (Erythrosine), FD&C Red number 40 (Allura Red), FD&C Yellow number 5 (Tartrazine), and FD&C Yellow number 6 (Sunset Yellow). All but Orange B are also approved for use in Europe, but in Europe, warning labels are now required on FD&C Red number 40 (Allura Red AC), FD&C Yellow number 5 (Tartrazine), FD&C Yellow number 6 (Sunset Yellow), and 3 colors used in Europe but not the United States: Quinoline Yellow, Carmoisine, and Ponceau. That study did not examine a restriction/elimination diet, however. Rather, they challenged typically developing children selected from the community with a drink containing a measured dose of food colors and a sodium benzoate preservative. The children were a cohort of 3 year olds ( $n = 153$ ) and a cohort of 8 year olds ( $n = 144$ ). The results were complicated by the use of 2 different formulations of active drink plus placebo, and the finding that in the 2 age groups different formulations influenced ADHD symptoms. Nonetheless, given the absence of nutritional benefit of the food additives and a precautionary stance, European regulators took action. This study seemed to support, indirectly, that an elimination diet therefore might help children with ADHD.

Another large European study, conducted in the Netherlands, also attracted considerable attention and some controversy. Pelsser and colleagues<sup>39</sup> conducted a double-blind crossover study of an elimination diet. They randomized 50 children with ADHD to an individually designed few foods diet and 50 to healthy diet counseling. Responders to the elimination diet were then given a challenge using high-inflammatory or low-inflammatory foods on the basis of each child's individual IgG blood test result. Thirty children (60%) had a positive response to the restriction/elimination diet, but only 19 of 30 had symptom relapse on the challenge foods. The authors concluded that their restriction/elimination diet was effective for ADHD but that the use of IgG blood test to determine who should be treated was not useful. Although findings appeared to be impressive, a critical flaw in the design was that the authors relied on clinician ratings for the primary findings, and clinicians in turn relied on parent reports—but parents were, of course, not blind to the interventions. Those same authors reported a brief review of prior trials of restriction diets in ADHD and

identified a large effect of  $d = 1.2$ . However, that effect relied on including nonblind, open-label trials.

Controversy continued in North America. In 2008, the Center for Science in the Public Interest, a consumer advocacy organization, petitioned the FDA to regulate food color additives. They provided an unpublished literature review arguing that colorings contributed to behavior problems and contended there was little justification for incurring any health risks, because food colors provide no health benefits.<sup>40</sup> The FDA subsequently commissioned its own unpublished, qualitative review, which concluded in 2011 that the evidence fell short of a causal association for food colors that are approved in the United States. However, that same year a major published qualitative review by Stevens and colleagues<sup>41</sup> (see Table 1) concluded that a subgroup of children with ADHD is sensitive to synthetic color additives, flavors, or salicylates and could benefit from a restriction/elimination diet. Thus, they highlighted not only the issue of differential response across different children but also the idea that restriction/elimination diets have value, and food coloring per se may not be the main culprit.

To further investigate all this quantitatively, Nigg and colleagues<sup>42</sup> conducted a meta-analysis of both restriction/elimination diet effects and food coloring effects on ADHD. They identified 6 restriction diet studies that used either a placebo-controlled diet challenge or a crossover design,<sup>29,39,43–45</sup> which in aggregate examined 195 children for improvement in hyperactive symptoms. However, one study<sup>39</sup> had questionable blinding of participants and was also a statistical outlier that fully accounted for heterogeneity of effects. Effects therefore were interpreted with the remaining 5 studies. These studies yielded a summed response rate (response being defined variously across studies) of **greater than 35%** (95% confidence interval [CI], 19%–52%;  $n = 164$ ). Because of the variable definition of responder across studies, the aggregate effect size on symptom change was examined. Pooling across all informants (parents, teachers, observers), the 5-study effect was  $g = 0.29$  (Standard error = 0.12 [95% CI, 0.16–0.52];  $P = .014$ ) with almost no variation across studies.

Sonuga-Barke and colleagues<sup>6</sup> identified a somewhat larger effect size in their meta-analysis by restricting studies to children who had a clear diagnosis of ADHD, as noted in Table 1. Stevenson and colleagues<sup>46</sup> distinguished between restriction elimination diet generally and elimination of food coloring. They concluded that both interventions might work, but that well-conducted large trials were lacking (foreshadowing the present authors' own conclusion to an extent).

When putting together both studies of restriction/elimination diets generally and studies of food color elimination specifically, effects sizes across the best studies therefore appear to range from  $d = 0.2$  to  $d = 0.4$  depending on study selection, with the possibility that effects are somewhat larger in children with ADHD. However, the finding of larger mean symptom changes in children with ADHD is difficult to interpret, because those children by definition have more extreme symptom scores and therefore less restriction of range in their scores in response to intervention. In addition, if food colors are not the main culprit in dietary effects, then challenge studies of food colors will underestimate the effects of an elimination diet.

Carter and colleagues<sup>47</sup> challenged children who had responded to an elimination diet with foods to identify what caused their symptoms to worsen. During these challenges, a wide range of foods provoked reactions, including typical allergenic foods (wheat, eggs, milk, cheese), chocolate, and additive-containing foods. Only a small minority of children seemed to react primarily to artificial colorings.

Furthermore, and crucially, the mean symptom change is of little interest when it comes to clinical decision-making: more important is likelihood of positive response. What percentage of children might respond? If responses are heterogeneous, then the mean symptom change may obscure a strong response in some children and no response in the others. This topic is discussed again below.

Thus, as should be apparent, a key challenge in evaluating this literature is that different reviewers do not agree on what the relevant set of studies is for a given question, simply because variation in study methodology is so vast. Evaluating response to diet is also complicated by a wide range of study designs and questions asked. The studies in the literature have asked the following questions and arrived at the following answers.

First, many studies simply asked, when an open-label few foods diet is given with no attempt to blind raters to the diet, what percentage of parents or other observers think their child has improved after a few weeks? Nigg and colleagues<sup>42</sup> pooled studies on this question and answered, “49%” as shown in modified form in Table 2. However, this number is not the number of randomly selected children with ADHD who will respond to diet—many of these studies drew children from specialty clinics for parents of children who either were interested in dietary intervention or already had suspected dietary problems. Others examined normal, nonhyperactive youth.

Two of these studies are considered in detail for the purpose of illustration. Rowe and Rowe<sup>48</sup> had 800 children referred for problems with hyperactivity. Of these 800, they selected 200 whose parents suspected that problems were related to diet (it was not clear if more than 200 parents suspected this, so a conservative estimate is that at least 25% of the parents thought diet might be affecting their child’s symptoms). These 200 then underwent an open-label, nonblind trial of a diet free of food colorings; fully 75% (150) of them saw improvement. Of these, 54 agreed to a double-blind, placebo-controlled trial in which 24 of 54 seemed to respond. From this study, it seems clear that some children respond to dietary intervention, but the prior probability of response for a given child with ADHD is very difficult to gauge. It is not 24 of 54, because many nonresponders were already screened out. An alternative inference might be that 150 of 800 were responders by parent report on open label, and that half of these were “genuine,” leading to an estimated true dietary response rate in the total ADHD population of 75 of 800 or about 9% to 10%, rather than the 49% in Table 2.

Carter and colleagues<sup>47</sup> provide another example. They selected 130 children referred to a specialty clinic for diet and hyperactivity (many already on special diets to address their ADHD). Each child was then placed on an individualized, open-label, nonblinded few foods diet for 2 to 3 weeks, with dietary adjustments made to maximize chances of improvement.



Only 78 (60%) were able to tolerate the 2- to 3-week few foods trial and continued. For 59 of them, parents thought there was meaningful improvement, suggesting an open-label response rate of 45% (59/130), but 9 of these were unable to continue the diet after the trial, leading to an open-label success rate of 38% even in children for whom parents suspected a dietary problem ahead of time. Foods were then reintroduced in an effort to identify offending substances or foods, again in a nonblind, open-trial fashion. Finally, 19 children who had been responders were given a double-blind, placebo-controlled trial with and without offending foods. This trial was done by disguising offending foods or food colors into the food. For 14 of 19 (73%) children, behavior was “better” on placebo, although size of the effect required to identify a change was unclear. From this study, it would be inferred that perhaps 28% ( $38\% \times 73\%$ ) of children whose parents suspect a dietary influence will have a true positive response to diet in regards to a reduction in ADHD symptoms, again less than the 49% implied in Table 2.

Second, then, is the question of a true double-blind trial to look at response rate. Because most studies have been preoccupied with mean symptom change, only a few studies meet the criteria of using an elimination diet, maintaining at least a single-blind (observers or raters are not aware of the diet) or a double-blind (parents, children, and observers are unaware of the diet), and also enable a count of percentage of responders by some definition. Nevertheless, these are the most informative if heterogeneity of response is assumed.

As noted earlier, Nigg and colleagues<sup>42</sup> concluded that the handful of available studies in this vein suggested a response rate that could be 25% to 30%. A conservative set of such studies is summarized in Table 3. (Table 3 excludes some studies that purported to be double-blind but which were judged not to be double-blind.) Table 3 suggests a response rate of about 26% of ADHD children to various forms of restriction diet. The authors considered these studies a bit more closely to scrutinize the clinical question of response likelihood and to illustrate the methods and range of findings.

Kaplan and colleagues<sup>29</sup> examined 24 hyperactive preschool boys. They controlled all food given to the entire family during the weeks of the trial, with a diet that restricted not only food colors, but also chocolate, MSG, preservatives, caffeine, and any substance that families reported might affect their specific child. The diet was also low in simple sugars, and it was dairy-free if the family reported a history of possible problems with cow’s milk. They defined a responder as 25% symptom improvement, and by this criterion, the response rate was nearly 50%.

Harley and colleagues<sup>44</sup> studied 36 school-aged children and 10 preschool children. Here only the school-aged children were considered because they were unable to obtain teacher ratings on the preschoolers (although there was some suggestion of a higher response rate in the preschoolers). They likewise removed all food from the house, delivered all food to the entire family, disguised the foods, and left the families unaware of what diet they were eating or which weeks they were eating the experimental diet. Thus, blinding of parents and teachers was carefully done. They defined a meaningful change as just a 10% change in the rating scale on the experimental diet. By this criterion, 30% of the mothers or fathers saw improvement. However, these effects tended to occur only when the experimental diet was

the second diet tried, raising suspicion of rater artifact. In teacher rating (perhaps the best single rater), there was no such order effect and only 6 of 36 or 17% showed a minimal 10% improvement. Only 4 of 36 (11%) showed a 10% improvement agreed on by both teacher and at least one parent.

Williams and colleagues<sup>49</sup> gave a full elimination diet in an open-label fashion, but then conducted a double-blind trial using cookies with additives in them, thus providing a lower bound estimate on response. They required a 33% change in symptoms to define a responder. By that criteria, 5 of 26 (19%) were responders in teacher ratings; none of these were echoed in parent ratings.

Schmidt and colleagues<sup>45</sup> created a reasonable attempt at a double-blind, placebo-controlled oligoantigenic diet for 49 children. The outcome was judged based on ratings in a standardized setting by trained raters blinded to intervention condition. Twelve (24%) children responded, but notably, the response magnitude in those 12 children was judged to be similar to the response magnitude of children who received medication in the medication arm of the same trial. This small study thus suggests that the diet may work very well for some children.

Overall, studies that fully control the diet and conduct a double-blind trial to evaluate response rate are exceedingly rare, small, and outdated (none have been reported in nearly 2 decades if the studies by Pelsser and colleagues are excluded for inadequate blinding). More common are double-blind trials of food color additives. Taken together, the literature suggests that some children respond, but are almost certainly a minority of children with ADHD.

## **SUMMARY OF LITERATURE ON EFFECTIVENESS OF RESTRICTION DIET FOR ADHD**

A small, but extensively discussed literature yields an emerging consensus that dietary intervention to remove food additives (color and perhaps preservatives) likely yields a small aggregate benefit, which is in the range of a standardized mean difference of about 0.3. Because this finding is based on a randomized, placebo-controlled trial, it verges on the strongest level of evidence rating (level 1) based on the guidelines from the Oxford Center for Evidenced Based Medicine. However, the small samples and now-dated methods of most studies, in conjunction with relatively small effect, suggest that the evidence rating might be conservatively graded at level 2. That said, and while the effect size of 0.3 is much smaller than a medication effect, it could be clinically significant in some cases. For example, a change of this magnitude across a group average is equivalent to a change from the 62nd to the 50th percentile.

Overall, for children presenting for ADHD treatment with no obvious gastrointestinal symptoms or strong prior evidence of a dietary effect, a strict elimination diet may have a 10% to 30% chance of providing a true effect detectable on a double-blind measurement, but this estimate is limited by very small samples and widely varying methods. The best estimate on the small literature is about a 25% rate of at least some symptom improvement.



For some children, perhaps a minority of 10% of children with ADHD, response can include a full remission of symptoms equivalent to a successful medication trial. In short, the literature suggests that an elimination diet should be considered a possible treatment for ADHD, but one that will work partially or fully, and only in a potentially small subset of children.

## LIMITATIONS AND RESEARCH DIRECTIONS

Two major limitations plague this literature and are noted by all reviewers. First, the data base is very small. In part, this is because doing these studies well is extremely difficult. Even if all elimination diet and food color challenge studies are taken as a whole, studies that used properly controlled procedures have examined only a few hundred children, and even fewer with ADHD. Much of this literature is in fact outdated, going back 3 decades. In the interim, understanding and assessment of ADHD have evolved; children's diets and average intake have changed, and the number of food additives used in the United States has increased. Thus, effects for today's children may look rather different than they did 30 years ago.

Furthermore, cultural and national differences in food content are notable, such that results in one nation may not generalize to another. For example, the number of food additives approved for use varies considerably between countries. Canada<sup>50</sup> and the European Union<sup>51</sup> both have less than 500 food additives approved for use. Contrast this with the United States, which has over 3000 food additives allowed to be used in food.<sup>52</sup> This much more liberal food policy results in a much larger exposure to chemicals in the United States. The issue of historical relevance is also notable, in that food content has changed. Stevens and colleagues<sup>53</sup> reported that the amount of artificial food colors and sweeteners allowed into foods has risen 5-fold in the past 60 years. This fact may suggest that prior studies have underestimated potential benefits for today's children, although there is as yet no evidence that the prevalence of ADHD differs among these nations.

The second major limitation is that the literature consistently shows that some children appear to respond to dietary intervention and some do not. Who are the responders, and how big is their response? This question has not yet received sufficient investigation to enable much beyond speculation given the very small, almost pilot nature of studies of individual differences to date. Although some studies suggested that response rate was predicted by parent suspicion of a dietary sensitivity, these effects were generally not formally defined, measured, or replicated. Thus, it is difficult to derive much clinical guidance from this research. Further comment is made in the "Future Directions" section.

## CLINICAL ISSUES RELATED TO ATTEMPTING A RESTRICTION DIET

With the preceding in mind, dietary intervention for ADHD has less than a 50–50 chance of success and a notably lower chance of success than treatments such as pharmacotherapy. Clinical advice to parents interested in a restriction/elimination diet for children with ADHD might take a form along these lines: "An elimination diet has a chance of success between 0% and 50%, with our best guess being a 10% to 30% chance of successful completion and positive response." However, patients would need to be advised of the risks and difficulties

of such interventions, including the risks of continued behavioral or learning problems, while other treatments which may have a 60% to 90% chance of benefit are delayed.

With that said, (1) many parents remain interested in dietary intervention, (2) the literature suggests that some children may benefit (a trial is not senseless), and (3), clinicians need some idea what the family would be getting into if they attempt a restriction diet. Therefore, a brief presentation of clinical considerations if such an intervention is going to be pursued follows.

First, a key issue for the mental health professional is often the lack of detailed nutrition education to adequately support a family embarking on an elimination diet. Each type of diet has different considerations based on potential difficulties with adherence and varying levels of safety. In general, elimination diets require discipline to sustain the diet over the testing period, major changes to food intake, and removal of highly palatable foods that are pleasurable due to their ability to release dopamine (high sugar-processed food)<sup>54,55</sup>; there is potential for conflict between parent and child if the child is unhappy with the dietary change. Thus, implementing these diets can be very challenging for the family and the clinician.

A “few foods” diet is by far the most challenging, because it is highly restrictive (initially allowing only a few foods with low allergenic potential) and then requiring testing of each food as it is reintroduced. Furthermore, the few foods diet must be overseen by a dietitian to ensure that the nutritional adequacy of the diet is maintained during the testing period. This dietary intervention is the most restrictive and the least nutritionally complete; therefore, it may be best viewed as a last resort option unless clear food allergy symptoms are present in addition to ADHD symptoms. At the same time, this diet can be very beneficial for identifying multiple food allergies in an individual. If a parent reports multiple known food allergies in their child and/or food allergy symptoms (described earlier) are present in addition to ADHD symptoms, then the few foods diet may be an appropriate place to start. Referral to an immunologist who can conduct skin prick allergy testing may also be beneficial, but dietary response may occur even with a negative skin prick test, if the response is due to a food intolerance rather than to an allergy. It remains unclear whether the presence of food allergy symptoms or allergy skin prick findings increase the likelihood that ADHD symptoms will respond to an elimination diet.

Second, if food allergy symptoms are *not* present, then a diet only restricting food additives may be a better choice. This diet is much less restrictive and hence is easier to implement and not as likely to cause an iatrogenic nutrient deficiency. Nonetheless, nutritional counseling is again advisable to ensure a nutritionally adequate diet is maintained during the trial and to counsel parents in learning how to read ingredient lists on food labels and how best to avoid food additives. In general, there is no risk to the exclusion of food additives per se, because most food additives, with the exception of vitamins and minerals, do not add nutritional value to the diet. Each food item in the diet can be replaced by a similar food item that excludes these additives. This concept helps prevent families from simply “excluding” foods. For example, a children’s brand of breakfast cereal high in artificial colors can be replaced by oatmeal with added brown sugar and raisins. This approach can

potentially steer the family toward a more whole-food, nutrient-dense diet that can increase their nutrient intake in addition to helping them avoid additives.

In short, a mental health professional can start this process, but generally should collaborate with a dietitian or other qualified professional with nutritional expertise. Patients can be given a list of food additives to avoid (for examples, see Appendix A) and can be instructed to look for ingredient labels that are short and easy to read and that have ingredients that they themselves could easily add to a food. For example, sodium benzoate would not be added by someone cooking at home, so that is an ingredient they would avoid.

It can be helpful to remind patients that nutrient-dense foods that have few to no additives are more often found on the outer aisles of a grocery store (fruits, vegetables, meat, dairy, and bread) and that bakery bread has the fewest additives. Other staple foods lower in additives can be found in the middle aisles (many times very low or very high on the shelves). These staples lower in additives include items like simple brown rice, oats, pasta, canned tomatoes, beans, nuts, and applesauce. Label reading will take more time initially, while safe foods are first being identified, and less time later.

With regard to duration, the diet can be tested over a 2- to 4-week period. It is important to emphasize that, to evaluate whether there is benefit of the diet, the diet must be followed strictly for a few weeks. Furthermore, during this period there is substantial possibility of placebo or expectancy effect, as would be seen with initiation of drug treatment. Regular standardized ratings (eg, using the 10-item Conners ADHD Index or Conners Global Index,<sup>56</sup> depending on target symptoms) could be obtained weekly, preferably from a teacher, in addition to the parent. A baseline rating should be obtained for a week or 2 before the trial. The mental health professional should review these ratings, score them, and examine them for reliable improvement, which means considering the 90% confidence interval around the scores (provided in the manual) to determine if the effect is likely to exceed chance variation in behavior. If after 4 weeks of strict adherence, no benefit is noted, then the patient could be switched to other treatments instead.

Note that there is one exception to the prior guideline. The few foods diet used for allergy testing does not follow this same time period. Allergy symptoms often remit within days of removing an allergen from the diet. Then, foods must be reintroduced individually over the next few weeks to test for a reaction. Therefore, if benefit is not noted after 1 week on the few foods diet, it can be discontinued.

## RECOMMENDATIONS

A major recommendation coming out of this review, echoing prior reviews (see Table 1), is that **dietary intervention for ADHD was abandoned too quickly in North America**. Although it is likely that only a minority of children with ADHD will respond to dietary intervention, the evidence persistently suggests that for some children such intervention can be quite effective. Thus, where should the field go to develop and realize this possibility? Several additional future study and design considerations and suggestions were offered by Stevenson and colleagues.<sup>46</sup> The present authors highlight selected recommendations of their own here.

The first key future direction is clearly the need to improve personalized selection or treatment matching. Here, there are several levels of analysis that need to be pursued. It has already been noted that prior, albeit small studies, attempted to select children on the basis of either (1) allergy symptoms, or (2) ADHD status. These types of clinical predictors need to be more carefully re-evaluated in the contemporary context. In addition, advances in biological measurements suggest the potential to examine bio-markers of treatment response that may be of value. As one illustration, Stevenson and colleagues<sup>57</sup> found that histamine degradation genes moderated the effects of food additives in the data set reported by McCann and colleagues.<sup>37</sup> Further efforts in research to evaluate other biomarkers (eg, inflammatory biomarkers) may be valuable as understanding of these mechanisms increases.

Thus, the effect of diet on ADHD, and the identification of who benefits, would be greatly aided by better understanding of mechanisms in the ADHD population. To date, attempts in this vein have not yielded convincing results. Pelsser and colleagues<sup>39</sup> failed to find reliable prediction of diet response and IgE levels in blood, and use of IgG levels to identify challenge effects was similarly inconclusive, leading those authors to conclude that such tests did not add clinical value. This finding also suggests that food intolerance may be more likely than food allergy in this population.

Nonetheless, it is increasingly recognized that dietary additives, unhealthy food, emotional stress, and chemical toxicants in the environment may act synergistically and via common mechanisms, including in some instances inflammatory pathways. Studies of mechanisms and efforts to preidentify future responders to a dietary intervention can readily measure or at least obtain relevant sampling of stress (self-reports as well as cortisol measures), toxicant burden (urine or blood samples), along with food studies. Although assaying all of these measures at once is costly, such data and tissue banks will ultimately be needed to ensure maximal benefit of tailored lifestyle-related treatment and prevention approaches for ADHD.

Second, what is striking is the small scale of this literature relative to popular interest. Needed are fresh contemporary trials of elimination diets with well-controlled double-blind procedures as were pioneered decades ago. Contemporary trials of elimination diets are particularly needed, for the current readership, in North America, where trials of elimination diets essentially have been at a standstill for a generation. The same holds true for any nation that wants to evaluate pertinence of elimination diets in children with ADHD in their nation's specific context.

Third, the interplay of food reactivity with basic nutrition is increasingly in need of scrutiny. A modified diet may also be more nutritious. Thus, examining nutrient intake and maximizing nutrition while eliminating potential food intolerances or allergies may yield the most powerful effects. At the same time, the fact that supplementing with nutrients may be less burdensome than a few foods diet trial may open alternative avenues for treatment-tailoring.

Finally, which symptoms respond? Twenty years ago, Rowe and Rowe<sup>48</sup> suggested that it might be emotional symptoms, such as irritability, rather than inattention or hyperactivity

that responds best to dietary intervention. This hypothesis has been often overlooked since then, yet may warrant renewed scrutiny in light of renewed and strong interest in the role of emotion regulation and irritability in ADHD.<sup>58</sup>

## SUMMARY

Two generations ago, ADHD was seen by many as a neurotic reaction to a difficult upbringing. A decade ago, it was seen as primarily a genetic condition by many. Now it is seen, more appropriately, as likely to be an epigenetic condition triggered, in susceptible individuals, by varying environmental amplifiers. For a subgroup of children, these appear to include food intolerance, food allergy, or both. The literature clearly demonstrates that a minority of children with ADHD will benefit from an elimination diet. Research funders, scientists, and clinicians would do well to re-invigorate investigation of this intervention, while avoiding both excessive skepticism (clearly, it may work for some), and excess optimism (it probably only works for a minority). If it can be determined who benefits and why, important insights into the pathophysiology of ADHD could result. Because of likely heterogeneity of response, studies should focus on identifying the rate of responders by an a priori definition of clinically significant response and then examining predictors of response.

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## APPENDIX A: EXAMPLE FOOD ADDITIVE LIST THAT COULD BE GIVEN TO A PATIENT

*Food additives to avoid:*

- All artificial colors
- All artificial flavors
- All artificial sweeteners, including aspartame, acesulfame K, neotame, saccharin, sucralose
- Sodium benzoate
- Butylated hydroxyanisole and Butylated hydroxytoluene
- Carrageenan
- Monosodium or monopotassium glutamate
- Any hydrolyzed, textured, or modified protein

**KEY POINTS**

- Food elimination diets come in different forms; the most restrictive or “few foods” diet eliminates a wide range of foods for a temporary period, adding foods back in one by one in an attempt to identify symptomatic triggers.
- Use of elimination diets to treat attention deficit and hyperactivity disorder (ADHD) has been proposed and studied for nearly 40 years and frequently reviewed and discussed.
- A consensus has emerged among most reviewers that an elimination diet produces a small aggregate effect but may have greater benefit among some children.
- Very few studies enable proper evaluation of the likelihood of response in children with ADHD who are not already preselected based on prior diet response. This critical question should be the focus of future studies.
- Future studies should be accompanied by examination of moderators of response (which children respond) and mediators (mechanisms, particularly physiologic mechanisms).

**Table 1**

Major reviews of ADHD and restriction/elimination diets

Authors, Year	Focus	Method	Conclusion
Kavale & Forness, <sup>35</sup> 1983	Feingold diet	Meta-analysis	ES = 0.11 (ns)
Breakey, <sup>59</sup> 1997	Diet generally	Qualitative	Some children
Schab & Trinh, <sup>36</sup> 2004	Food colors	Meta-analysis	ES = 0.21* (parent)
Stevens et al, <sup>41</sup> 2011	Diet generally	Qualitative	Some promise
Pelsser et al, <sup>39</sup> 2011	Restriction	Meta-analysis	ES = 1.2*
Nigg et al, <sup>42</sup> 2012	Restriction	Meta-analysis	ES = 0.30*
Nigg et al, <sup>42</sup> 2012	Food colors	Meta-analysis	ES = 0.22*
Sonuga-Barke et al, <sup>6</sup> 2013	Restriction	Meta-analysis	ES = 0.51 (ns)
Sonuga-Barke et al, <sup>6</sup> 2013	Food colors	Meta-analysis	ES = 0.42*
Arnold et al, <sup>60</sup> 2013	Diet generally	Qualitative	Some promise
Stevenson et al, <sup>46</sup> 2014	Diet generally	Qualitative	Some promise

Abbreviation: ES, effect size.

\* p<.05

**Table 2**

Open-label, non-blind trials of restriction/elimination diet of any type (colors only, few foods, other) on variously defined symptom response rate of children with ADHD

Study Name, Year	N	Rate (%)	LL (%)	UL (%)	P Value
Cook & Woodhill, <sup>61</sup> 1976	10/15	67	41	85	.206
Rapp, <sup>62</sup> 1978	12/23	52	32	71	.835
Conners (Ch 3), <sup>63</sup> 1980	27/63	43	31	55	.258
Conners et al (Ch 4), <sup>70</sup> 1980	14/37	38	24	54	.143
Conners et al (Ch 5), <sup>71</sup> 1980	38/54	70	57	81	.004
Holborow et al, <sup>64</sup> 1981	29/344	8	6	12	.000
Egger et al, <sup>43</sup> 1985	62/76	82	71	89	.000
Loblay, <sup>65</sup> 1985	6/14	43	21	68	.594
Rowe, <sup>66</sup> 1988	14/55	25	16	39	.001
Sarantinos et al, <sup>67</sup> 1990	9/13	69	41	88	.177
Breakley et al, <sup>68</sup> 1991	281/516	54	50	59	.043
Carter et al, <sup>47</sup> 1993	50/130	38	31	47	.009
Boris & Mandel, <sup>69</sup> 1994	19/26	73	53	87	.024
Rowe & Rowe, <sup>48</sup> 1994	150/800	19	16	22	.000
Pelsser et al, <sup>21</sup> 2009	11/15	73	47	90	.083
Pelsser et al, <sup>39</sup> 2011	32/50	64	50	76	.051
Total	764/2231	49	36	63	.924

— 25% after liberalization and diet abandoned by most but 40 improved on diet ..... 73%

410 responded: 410/516 = 79.5%

**Table 3**

Summary of 5 double-blind randomized trials of elimination or challenge diet in children with ADHD not preselected to be diet responsive

Authors, Year	Criterion (%)	N	Rate (%)	LL (%)	UL (%)
Conners et al. <sup>72</sup> 1978	25	15	26.7	10.4	53.3
Harley et al. <sup>44</sup> 1978	10	23	22.8	12.6	37.8
Kaplan et al. <sup>29</sup> 1989	25	24	41.7	24.1	61.7
Schmidt et al. <sup>45</sup> 1997	100	49	24.5	14.5	38.3
Williams et al. <sup>49</sup> 1978	33	24	19.2	8.2	38.7
Pooled effect		135	26.4	20.0	34.1

N=36; N=10

10 of 24 = responders on narrow definition; another 4 were "mild responders"

12 of 49 children improved

Note: Change criterion reflects change in symptom scores identified as necessary by investigator to say child benefitted from intervention. 100% symptom change means "normal range" behavior after intervention. All except Schmidt used Conners rating scale as the outcome measure. LL, UL, 95% confidence interval upper and lower limits.