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LEADING ARTICLE

Broad-Spectrum Micronutrient Treatment for Attention-Deficit/Hyperactivity Disorder: Rationale and Evidence to Date

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Abstract Attention-deficit/hyperactivity disorder (ADHD) is a chronic psychiatric illness, which often co-occurs with other common psychiatric problems. Although empirical evidence supports the short-term efficacy of pharmacological and behavioural treatments, families often search for alternative treatment methods because of concerns about side effects and safety, cost and access, as well as fears about long-term exposure to psychotropic medications. This review presents the published evidence on use of broad-spectrum micronutrients to treat ADHD symptoms. This approach makes physiological sense in that nutrients are required for many critical biochemical reactions to occur, ranging from manufacturing neurotransmitters, to providing the mitochondria with essential nutrients for energy production, to assisting the gut to heal from inflammation. Multi-nutrient treatment approaches are an intriguing yet under-researched area; all but one of the trials conducted in the last decade have shown benefit for the treatment of ADHD symptoms, and the one negative trial likely used doses too low to effect change. However, the methodologies have varied widely from case-controlled studies to open-label trials to one randomized controlled trial. Sample sizes have typically been modest, although the effect sizes have tended to be medium to large. What is required now is replication, as well as investigation into the optimal ingredient range and optimal doses of nutrients. We discuss the proven and potential benefits of the broad-spectrum nutrient approach, considering the heterogeneous nature of ADHD.

Key Points

There is a good theoretical rationale for using broad-spectrum nutrient formulas for the treatment of attention-deficit/hyperactivity disorder (ADHD); however, the research base is still in its infancy

More research and replication are required to support preliminary positive findings of studies using micronutrients for the treatment of ADHD

There is great variability in ingredients and doses across studies, making comparisons challenging—consistency may need to be considered in future studies

1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders, reported to have been known since 1775 [1] and characterized by problems with inattention, hyperactivity and impulsivity [2]. It is now accepted that ADHD can be a chronic condition across the lifespan [3]. Worldwide prevalence rates are estimated at 5.29 % [4], and it is now thought that as many as 4–5 % of adults may suffer from ADHD [5, 6]. Overall, it is viewed as treatable but not curable; its heterogeneous aetiology and symptom expression complicate the effectiveness of those treatments that are available.

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Stimulant medications such as methylphenidate (Ritalin), pemoline (Cylert) and dextroamphetamine (Dexedrine), with or without cognitive–behavioural therapy, are the most common and most studied treatments for ADHD [7, 8]. The lack of evidence of long-term efficacy [9] and the side effects associated with these pharmacological treatments have led many consumers and researchers to look at other treatments for this chronic condition [10, 11].

2 Rationale for Investigations into Vitamins and Minerals to Treat ADHD

There has been a resurgence of interest over the last decade regarding the effects of diet and nutrient interventions on ADHD symptoms [12]. Dietary studies have investigated the impact of food additives such as dyes [13, 14], restrictive elimination diets [15], the impact of sugar [16, 17] and other food sensitivities [18], dietary patterns such as the relationship between the Western/healthy dietary pattern and ADHD symptoms [19–21], and the role of early malnutrition on the expression of illness [22]. While diet manipulation may be an attractive way forward and may be necessary for a significant minority of children who do have specific food allergies or intolerances, it is not always viable, given the challenges associated with changing people's eating habits. Also, the effect sizes are typically modest and therefore less likely to benefit a large proportion of children [15]. Further, as some foods that children may react to include unprocessed items such as grapes, eggs and oranges, dietary restriction can lead to an unbalanced diet with the risk of micronutrient deficiencies [23].

Supplementation studies have largely focused on the effects of essential fatty acids (EFAs) on ADHD behaviours and, despite early positive trials (e.g. [24]), more recent reviews have determined that the benefit of fatty acids for ADHD is likely to be modest [25–27]. Trials of treatment with micronutrients (i.e. vitamins and minerals) have been varied but, for the most part, focused on single nutrients, often resulting in modest to negligible effects [28–30], suggesting that single nutrient interventions do not have an adequate impact on the complex array of biochemical pathways that may be aberrant in people with ADHD. For example, studies investigating single nutrients such as iron [31], magnesium [32, 33] and zinc [34, 35] to treat ADHD have shown mixed and inconsistent effects across reports [28–30]. This inconsistency is possibly because administration of one nutrient could cause an imbalance in other nutrients, and also because one nutrient is unlikely to resolve all vulnerabilities present in a complex disorder such as ADHD. It is reasonable to consider that a more viable way forward is to combine nutrients to mimic the whole array of nutrients required for optimal brain functioning.

The physiological mechanisms underpinning a multinutrient approach are likely very complex. For instance, there are many metabolic steps in every neurotransmitter pathway, which involve synthesis, uptake and breakdown. Each of those steps requires enzymes, and every enzyme is dependent upon multiple co-enzymes (cofactors), most of which require the presence of adequate quantities of vitamins and minerals. Some micronutrients, such as zinc, are also an essential part of the structures of some enzymes. One possible mechanism underlying psychiatric symptoms such as those seen in ADHD is inborn metabolic dysfunction, which limits the availability of vitamin and mineral cofactors, resulting in slowed metabolic activity [36, 37]. It has been shown with other physical disorders that impaired brain metabolic activity is correctable through nutrient supplementation [37]. In other words, broad-spectrum nutrient treatment may provide micronutrients in sufficient quantity that even enzymes with drastically reduced activity become so supersaturated with the necessary cofactors that near-normal function is restored [37].

Nutrients have many other roles in brain function that could explain their potentially therapeutic effects. For instance, improved energy metabolism of neurons and glial cells [38], which are under the direct control of the mitochondria in those cells, are very dependent on availability of nutrients. Mitochondrial disorders are characterized by decreased production of cellular energy in the form of adenosine triphosphate (ATP). Emerging literature shows that the manufacture of ATP is possibly compromised in ADHD, as well as in other mental disorders [39–41]. Brain tissue, in particular, requires a high level of ATP for metabolism, including the production of neurotransmitters, maintenance of the transmembrane potential, signal transduction and synaptic remodelling. Minerals such as magnesium and calcium, as well as several B vitamins, are required for aerobic metabolism and play vital roles as cofactors in the degradation of blood glucose via glycogenesis, the citric acid cycle and the respiratory chain in the mitochondria [42]. The so-called classical mitochondrial diseases (usually characterized primarily as musculoskeletal diseases) are often treated with nutrient 'cocktails' to increase mitochondrial function [43]; interestingly, most of these cocktails contain several key micronutrients, such as the antioxidant vitamins A, C and E, as well as coenzyme Q10 and creatine. However, the applicability of mitochondrial 'cocktails' to psychiatric disorders has not yet been demonstrated.

Another component of physiological function that is strongly dependent on vitamins and minerals, and is relevant to ADHD, involves digestion. The gastrointestinal

tract is one of the most energy-dependent, and thus vulnerable, organs in mitochondrial disorders, and its health is essential for proper nutrient absorption and function. Various mental problems have been reported in coeliac disease [44], an immune-mediated disease triggered by ingestion of gluten, which results in inflammation of the small intestinal mucosa, with ensuing malabsorption. A growing body of research is uncovering the important role that inflammation may play in the expression of psychiatric illness [38].

In summary, in-born errors of metabolism, likely causing increased metabolic need for nutrients, mitochondrial dysfunction, gastrointestinal inflammation and/or gut sensitivities, all point to the role of malabsorption and/or deficiencies of vitamins and trace elements in the expression of some psychiatric symptoms. This review evaluates the status of the scientific literature on use of combinations of nutrients for the treatment of ADHD.

3 Evidence for Micronutrient Treatment

Research with multi-ingredient formulas in the treatment of ADHD is relatively rare, although such combination therapies have been found to be effective in the treatment of low mood, cognitive deficits, stress, anti-social behaviour and disruptive behaviour [45–49]. Over the last decade, there has been a slow increase in the number of publications on multi-ingredient micronutrient formulas for the treatment of ADHD, with potentially more promising results than single-ingredient studies; however, well-controlled trials are still few. One reason for this lack of research may be that studies in the 1970s and 1980s found that vitamins given in inappropriate 'megadoses' (100 times the recommended daily intake) were not effective in the treatment of ADHD and were sometimes harmful at such high doses [50]. Perhaps because of those studies, as well as the overall short-term success of stimulant medications in controlling ADHD symptoms, interest in this line of research waned, as demonstrated by the small number of studies on broad-spectrum treatment published prior to 2000.

We recently conducted a systematic review on the use of broad-spectrum micronutrient formulas [51] for the treatment of all psychiatric symptoms. In this current review, we discuss the studies we identified that used broad-spectrum micronutrients for the treatment of ADHD, and we have also updated the search since 2013. (See Rucklidge and Kaplan [51] for details of the systematic review.) Table 1 provides details of clinical trials using broad-spectrum micronutrients of known doses to treat ADHD.

The first study to look at the impact of broad-spectrum micronutrient supplementation on ADHD symptoms was completed by Kaplan and colleagues over a decade ago [52]. They conducted an open-label trial in children with a variety of psychiatric disorders, including ADHD, bipolar disorder, anxiety, oppositional behaviours and Asperger's disorder. Six of the 11 children in the trial had ADHD, although one of these dropped out. After 16 weeks of taking a supplement, distributed under the name of EM-Powerplus™ (consisting of 14 vitamins, 16 minerals, 3 antioxidants and 3 amino-acids), all 10 of the children were rated as significantly improved in attention, anxiety, aggression, delinquency and mood. Few adverse effects were reported, and those that did occur were mild in all except two of the children, who were concurrently taking psychiatric medications. The trial was limited by the potential for observer and placebo/expectancy effects.

A few years later, a case-comparison study was published, in which Harding et al. [53] compared methylphenidate with broad-spectrum micronutrient treatment of ADHD symptoms in 20 children over a 4-week period. Co-occurring diagnoses and use of other medications served as exclusion criteria. The dietary supplement consisted of many nutrients (taurine, glutathione, alpha lipoic acid, garlic extract, glycine, 5 amino acids and 13 minerals), presumed gastrointestinal and immune support (*Lactobacillus acidophilus* and bifidus, lactoferrin and silymarin), EFAs, phospholipids, iodine, tyrosine, all of the B vitamins and some phytonutrients. With 10 children per group (based on parental choice), both groups showed significant improvement in neurocognitive tests, which measured auditory response control, auditory attention, visual attention and visual response control. The nutrient group did as well as the methylphenidate group; however, there were no measures of behavioural change in ADHD symptoms, and the sample size may have been too small for detection of group differences.

In the same year, Patel and Curtis [54] reported an open-label observational study with an even more comprehensive approach. Ten children with both ADHD and autism were treated for 3–6 months with vitamins (A and B complex), seven minerals, coenzyme Q10, amino acids and peptides, some EFAs, milk thistle, α-lipoic acid, digestive enzymes and probiotic bacteria. In addition, the parents of these children received instructions on controlling environmental factors (i.e. mites, exposure to toxins, pesticides and cleaners), gastrointestinal support, an organic diet, antigen injection therapy (to address dust mite allergens, foods, moulds and chemicals), chelation therapy and injection 1–3 times per week with glutathione and methylcobalamin (vitamin B_{12}). The researchers reported that on parental questionnaires, there was an 'average' improvement in concentration and attentional problems and hyperactivity-related problems; however, the study was severely limited in that it did not report on clinical improvement, nor did it include any statistical analyses or

Table 1 Intervention studies with broad-spectrum formulas for attention-deficit/hyperactivity disorder (ADHD)

Micronutrient intervention (daily dose)	Medication-free	Sample (age)[a]	Design	Length of trial	Results	Effect	Reference
Supplements supplied by a nutritionist including 1 multi-vitamin containing 22.5–27.5 mg vit B_1, 22.5–27.5 mg vit B_2, 75–140 mg vit B_3, 50–70 mg vit B_5, 43–86 mg vit B_6, 435–760 μg vit B_9, 90–175 μg vit B_{12}, 20–400 μg vit H, 140–200 IU vit E, 750–1,000 mg vit C, 2,000–4,500 IU vit A, 40–100 IU vit D_3, 20 μg vit K, 75–150 mg royal bee jelly, 10 mg dimethyl glycine, 10–20 mg citrus bioflavonoids, 5 mg grape seed, 20 mg bilberry extract, 20 mg soy constituents; multi-mineral containing 220–480 mg Mg, 110–170 mg Ca, 46–70 mg K, 140–200 μg Cr, 26–32 μg Se, 9–15 mg Zn, 2.5–4 mg Mn, 25–150 μg I, 1,200–1,800 μg B, 1.2–2.4 mg Cu, 4 mg Si, 5–40 μg Mo, 2–20 μg V, 1–2 mg Fe; amino acids including 275–425 mg taurine, 900–1,800 mg tyrosine, 700–1,830 mg glycine, 25–75 mg methionine, 0–10 mg *N*-acetylcysteine, 0–25 mg L-cysteine, 20 mg glutathione, 5 mg alpha lipoic acid, 900–1,800 mg tyrosine, 25–75 mg histidine, 600–1,400 mg glutamine, 25–75 mg alpha ketoglutarate, 30 mg L-carnitine, 200 mg garlic extract; *Lactobacillus acidophilus* and bifidus, 5 mg lactoferrin, 5 mg silymarin; EFAs including 180 mg EPA, 120 mg DHA, 45 mg GLA, 50–150 mg phosphatidyl choline; 20–25 mg inositol, 2.5–7.5 mg choline bitartrate	Yes in the nutritional arm of the study	$n = 20$ children with ADHD (7–12 y)	Parent choice of either 5–15 mg methylphenidate 2–3 times daily ($n = 10$) or nutritional supplement ($n = 10$)	4 wk	Both groups benefited as measured by neurocognitive tasks; no group differences	Treatment benefit	Harding et al. [53]
15 capsules (5 three times daily) of EMPowerplus™ formula[b]	No—5 of the children were concurrently taking medications (antipsychotics, antidepressants, stimulants)	$n = 11$ children with mood and behavioural problems including 5 with ADHD; 63.6 % boys (8–15 y)	OL	16 wk	Significant improvement on 7 of 8 CBCL scales, including attention; significant improvement in measures of mood, large effect sizes	Treatment benefit	Kaplan et al. [52]

Table 1 continued

Micronutrient intervention (daily dose)	Medication-free	Sample (age)[a]	Design	Length of trial	Results	Effect	Reference
EMPowerplus™ formula[b]	No—76 % (decreased to 38 % by the end of 6 mo) of those with ADHD and BD were taking medications concurrently; 41 % (decreased to 12 % by the end of 6 mo) of those with only ADHD were taking medications	$n = 120$ children and adolescents with bipolar disorder—24 % also had ADHD; $n = 41$ with ADHD only	Database analysis	6 mo	Decrease in bipolar symptoms from baseline (46 % lower than baseline); 46 % had >50 % improvement at 6 mo; results were similar with children who had both BD and ADHD; 43 % decline in PBD symptoms (effect size = 0.72) and 40 % in ADHD symptoms (effect size = 0.62). The ADHD-only sample showed a 47 % reduction in symptoms from baseline to LOCF (effect size = 1.04)	Treatment benefit	Rucklidge et al. [57]
EMPowerplus™ formula[b]	Yes—minimum 4 wk	$n = 14$ adults with ADHD (>18 years)	OL with 2 mo natural extension	8 wk	Improvement in all outcome measures, including attention, hyperactivity, impulsivity, depression, anxiety and stress (all large to very large effect sizes). At 2 mo follow-up, for those who stayed on, further improvement was noted, while those who stopped showed regression towards baseline	Treatment benefit	Rucklidge et al. [56]
6 LC-PUFA capsules containing 93 mg EPA, 29 mg DHA, 10 mg GLA, 1.8 mg vit E; *or* the above plus 1 chewable tablet of Blackmores containing 175 IU vit A, 700 μg vit B_1, 1.1 mg vit B_2, 12 mg vit B_3, 2.7 mg vit B_5, 1.3 mg vit B_6, 100 μg vit B_9, 1.5 μg vit B_{12}, 60 mg vit C, 100 IU vit D_3, 6 IU vit E, 50 μg vit H, 33.9 mg Ca, 7.5 mg Fe, 8.32 mg Mg, 77 μg Mn, 178.6 μg Cu, 118 μg K	Yes—minimum 3 mo	$n = 132$ children with ADHD, 46 % boys (7–12 y); 104 completed	DBRCT with 3 arms (placebo [$n = 27$], PUFA [$n = 36$], PUFA + Blackmores [$n = 41$]) followed by 15 wk single-blind extension	15 wk + 15 wk extension	Both active treatment groups (no difference between groups) greater than placebo on parental measures of inattention, hyperactivity, impulsivity, switching and controlling attention; no change on teacher ratings	No additional treatment benefit of micronutrients	Sinn and Bryan [55]

Table 1 continued

Micronutrient intervention (daily dose)	Medication-free	Sample (age)[a]	Design	Length of trial	Results	Effect	Reference
EMPowerplus™ formula[b]	Yes—minimum 4 wk	*n* = 80 adults with ADHD; 72 completed	DBRCT with two arms (placebo [*n* = 38] and active [*n* = 42])	8 wk RCT + 8 wk OL	Intent-to-treat analyses showed significant between-group differences favouring micronutrient treatment ($p < 0.05$) for CAARS DSM-IV total symptom subscales on self-ratings and observer ratings, but not on clinician scores. However, clinicians' CGI ratings favoured active treatment over placebo: 'much' or 'very much' improvement was seen in 48 % on micronutrients versus 21 % on placebo	Treatment benefit	Rucklidge et al. [61]

[a] *n* refers to the number of participants enrolled in the study

[b] EMPowerplus™: a 36-ingredient formula containing 5,760 IU vit A, 600 mg vit C, 1,440 IU vit D, 360 IU vit E, 18 mg vit B_1, 13.5 mg vit B_2, 90 mg vit B_3, 21.6 mg vit B_5, 36 mg vit B_6, 1,440 μg vit B_9, 900 μg vit B_{12}, 1,080 μg biotin, 1,320 mg Ca, 13.74 mg Fe, 840 mg P, 204 μg I, 600 mg Mg, 48 mg Zn, 204 μg Se, 7.2 mg Cu, 9.6 mg Mn, 624 μg Cr, 144 μg Mo, 240 mg K, 20.7 mg germanium sesquioxide, 2,400 μg B, 1,194 μg V, 29.4 μg Ni, 54,036 mg choline bitartrate, 360 mg DL-phenylalanine, 240 mg citrus bioflavonoids, 180 mg inositol, 180 mg L-glutamine, 60 mg L-methionine, 36 mg gingko biloba, 45 mg grape seed extract

ALA alpha linolenic acid, *B* boron, *BD* bipolar disorder, *Ca* calcium, *CAARS* Conners Adult ADHD Rating Scale, *CBCL* Child Behaviour Checklist, *CGI* clinical global impression, *Cl* chloride, *Cr* chromium, *Cu* copper, *DBRCT* double-blind randomized controlled trial, *DHA* docosahexaenoic acid, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders: Fourth Edition, *EFA* essential fatty acids, *EPA* eicosapentaenoic acid, *Fe* iron, *GLA* gamma linolenic acid, *I* iodine, *IU* international units, *K* potassium, *LC* long-chain, *Li* lithium, *LOCF* last observation carried forward, *Mg* magnesium, *Mn* manganese, *Mo* molybdenum, *Ni* nickel, *OL* open-label trial, *P* phosphorus, *PBD* paediatric bipolar disorder, *PUFA* polyunsaturated fatty acids, *RCT* randomized controlled trial, *RDA* recommended dietary allowance, *Se* selenium, *Si* silicon/silica, *V* vanadium, *vit A* beta-carotene/retinyl palmitate, *vit* B_1 thiamine, *vit* B_2 riboflavin, *vit* B_3 niacin/nicotinamide, *vit* B_5 pantothenic acid, *vit* B_6 pyridoxine, *vit* B_9 folic acid/folate, *vit C* ascorbate/ascorbic acid, *vit D* vitamin D_3/cholecalciferol, *vit E* d-alpha tocopheryl succinate, *vit H* biotin, *Zn* zinc

use standardized measures of behaviour. It also did not specify the doses of the nutrients that were used.

Sinn and Bryan [55] conducted a three-arm study comparing EFAs, EFAs with an over-the-counter multivitamin/mineral tablet (Blackmore's) and placebo. They did not find any additive benefit of the combined regimen over the EFA-only regimen; however, they acknowledged that the dose of the micronutrients may have been too low to reach any conclusions about specific ingredients in the tablet. Those in both groups taking EFAs benefited more than the placebo group in terms of improvement in ADHD symptoms (both attention and hyperactivity/impulsivity) and parental report of cognitive problems.

Another open-label trial using EMPowerplus™ in 14 adults with ADHD and mood instability showed significant improvement over 8 weeks in all ADHD symptoms (although problems with inattention were less well controlled than hyperactivity and impulsivity), as well as stabilization of mood in all participants in the trial [56]. A database analysis of 41 children with ADHD taking this same formula found that there was a significant improvement in ADHD symptoms studied over a 6-month period [57]. A number of case studies have also demonstrated on–off control of ADHD symptoms in a within-subject crossover design with this same micronutrient formula [58–60].

There is now one completed randomized controlled trial (RCT) using micronutrients to treat ADHD. Rucklidge et al. [61] studied 80 adults with ADHD randomized to receive either EMPowerplus™ ($n = 42$) or placebo ($n = 38$) and found that micronutrient treatment induced statistically robust improvements in several indices, from ADHD symptoms to global assessment of functioning, compared with placebo, with effect sizes ranging from 0.46 to 0.67. Specifically, the participants taking EMPowerplus™ reported greater improvement in both inattention and hyperactivity/impulsivity, as compared with placebo. Improvement in hyperactivity/impulsivity was also noted by the observers (usually a spouse or partner). Clinician ratings did not reveal group differences on the ADHD rating scales, but clinicians did report greater improvements in the global assessment of functioning, mood and clinical global impression. After 1 year post-baseline, as a group, these participants either stayed the same or regressed only slightly as compared with the end of the open-label phase, and they did not revert back to their baseline functioning [62]. The naturalistic follow-up also highlighted the likelihood that individuals will stay on a micronutrient treatment following trial participation. Although only 20 % of the participants who were followed continued to take the nutrients, as a group their ADHD symptoms were reduced into the nonclinical range, whereas the participants who stopped taking the nutrients or switched to medications were performing significantly worse on ADHD measures [62].

While trial length varied considerably across these positive studies (from 4 weeks to 6 months), all except the study by Sinn and Bryan used a broad spectrum of micronutrients (36–55 ingredients) at higher than recommended daily allowance (RDA) doses but lower than the level identified as being toxic [also known as the upper level (UL)], suggesting that the doses and breadth of ingredients are important in effecting change in ADHD symptoms. Of course, the doses cannot be too high, as they can then become toxic with no associated benefit, as demonstrated by the earlier studies that gave megadoses [63] of a small number of vitamins, usually with no accompanying minerals.

4 Directions for Future Research

Mainstream medicine has accepted the notion that pharmaceuticals are the preferred approach to the treatment of ADHD. However, as researchers and clinicians become increasingly aware of less than optimal efficacy rates in the long-term, as well as concerning side effects of these medications [9], there is a compelling reason to explore and properly evaluate other options. This review reveals there is potential benefit from nutritional approaches that employ a broad spectrum of vitamins and minerals, but much more research is required. One interesting theme that emerged was that, until recently, researchers typically studied individual nutrients (with limited success) rather than using a broad-spectrum approach with multi-ingredient formulas. Given that physiological function is best optimized by having all systems in balance, since different vitamin and mineral levels affect the absorption and effectiveness of each other, one needs to challenge the more conventional single-nutrient methodology [64].

Research on multi-nutrient treatment of ADHD is in its infancy. The multi-ingredient trials reviewed here all showed promise, but most suffered from lack of controls, small sample sizes, varied sampling procedures and inclusion criteria, and multiple assessment methods. No safety concerns were raised in any of the trials, and the evidence suggests that at least in the short-term, the nutrients do not have any negative impact on functioning [65]. Side effects are also typically minimal. The one RCT brings the level of rigour necessary for the field to advance and be taken seriously; however, replication and longer-term studies are now required.

The impact of diet alongside nutrient supplementation also needs to be considered. Although dietary pattern and socioeconomic status were not identified as predictors of response to nutrients in one study [66], it is unknown

whether a change in diet alone could achieve the same results as those obtained using nutrients. Given that there is an association between the Western dietary pattern and ADHD [19], it is worth investigating these associations further. Also, it is unclear whether these doses of nutrients can be used safely with medications [67], and caution must be applied if using medications and nutrients together—often the dose of medications can be reduced with continued beneficial effects on symptoms [68].

One striking feature of the research employing these broad-spectrum formulas is that the intervention is generally seen as being the primary intervention, whereas studies of single ingredients tend to be conceptualized as being supplementary to medications. Future research needs to address the question of whether there are certain nutrients that appear to be essential for positive benefit to occur. Certainly, some B vitamins are common across all formulas, although the doses can vary greatly. It is unknown whether large combinations of nutrients are essential for all individuals or whether subgroups of the nutrients might be sufficient for some people, depending on specific deficiencies. While Rucklidge et al. [66] did look at moderators of treatment response within a subsample of adults with ADHD who completed at least 8 weeks of exposure to the micronutrients, with good compliance, only one variable—the baseline ferritin level—proved to be useful in predicting who would respond. Higher baseline ferritin levels predicted who would be classified as an ADHD responder, suggesting that those with healthy iron stores were more sensitive to the broad-spectrum formula. It is also worth noting that high ferritin levels can reflect inflammation [69] and, therefore, perhaps the micronutrients decreased inflammation and thereby improved ADHD symptoms [70]. Baseline serum levels of copper, zinc, vitamin B_{12}, folate and iron did not influence the response to the broad-spectrum formula, suggesting that peripheral changes in blood levels may not be useful in determining what is occurring in a metabolically active brain [71].

It is unrealistic to expect all studies of broad-spectrum formulas to use the same compound, but the variability across studies presents a challenge for interpretation. Future trials comparing compounds may assist us in understanding the importance of various nutrient combinations and doses. Perhaps modern metabolomics methods, providing detailed metabolic information at the cellular level, will eventually provide the tools for biological subclassification of patients within the present-day criteria-based psychiatric diagnoses. This type of information may facilitate identification of more personalized approaches for individuals, perhaps leading to an array of potential nutrient treatments based on individual profiles. It may also aid in determining whether there is a subset of individuals most likely to benefit from this treatment, given that not all patients respond to the micronutrients.

There are several methodological improvements that should be attended to in future studies. Trials would benefit from reporting on pretreatment nutrient levels for as many nutrients as possible, even though such information would be based on peripheral blood and might not be excellent at indicating levels in the brain. Three-day food records could be analyzed to evaluate the diets of the treated groups, as it is possible that food intake may influence the response to treatment. Symptoms and disorders need to be well documented for the samples being studied, as well as co-occurring physical disorders that may impact the treatment response, such as Crohn's disease or coeliac disease. We anticipate that a healthy gastrointestinal system will be increasingly considered as essential for maximizing the treatment response to micronutrients, and researchers may consider adding probiotics to micronutrient treatment to optimize nutrient absorption. Research on the fascinating role that the intestinal microbiota play in the expression of psychological symptoms is burgeoning [72–74] and will likely interest mainstream mental health professionals as research decodes more of the gut–brain connections [75].

It may seem implausible that the broad-spectrum nutrient approach would have an effect across a broad range of psychiatric symptoms; however, as research continues to uncover the interaction between the environment (including nutrient intake) and genes (e.g. [76]), this approach should prove logical and scientifically sound. If it is found that micronutrients can positively affect the symptoms of many types of psychiatric symptoms, *or can even prevent the onset of such symptoms* (as has been shown using EFAs for prevention of psychosis [77]), the research will do more than contribute to improved treatments for mental disorders. The larger impact could be the development of aetiological models that include nutrition more centrally to complement the myriad of existing models ranging from exposure to environmental toxins to genetics to family functioning [78]. Also, if the results are replicated consistently, then a new treatment option would become available for those families seeking another approach to the management of ADHD symptoms.

The implicit hypothesis underlying the primary use of multiple micronutrients for amelioration of mental symptoms is that *mental illness may be a manifestation of suboptimal nutrition.* This hypothesis must be seen in relation to the individual's genetically determined nutrient needs for optimal brain metabolic activity. This new hypothesis of the origins of mental illness can actually be traced to 20th-century ideas [79], but it is not yet proven according to 21st-century standards. The use of broad-spectrum micronutrient formulas is a promising approach with sound theoretical reasons for their beneficial effects on

psychiatric symptoms. And with respect to ADHD, this review demonstrates that the growing body of literature on micronutrient treatment is compelling enough to provide the impetus to conduct trials in mental disorders routinely.

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