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A Nutrigenomic Coenzyme/Cofactor Monotherapy for Pediatric ADHD

Jaimee Arroyo[1], Jordan Miller[1], Kayla Sangrey[1], Zeke Nadeau[1], Moriah Olson[1], Esther Bargatze[1], Luciana Muñoz[1], Emily Kay[2], Andrew Farah[2*]

[1]Hopewell Family Care, 5045 Old Hickory Blvd #203, Hermitage, TN 37076, USA

[2]High Point University 1 N University Pkwy, High Point, NC 27262, USA

***Corresponding author:**
Andrew Farah

bfarah@highpoint.edu

High Point University 1 N University Pkwy, High Point, NC 27262, USA

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Abstract

The most encountered neurodevelopmental condition in childhood is Attention Deficit Hyperactivity Disorder (ADHD), affecting roughly one in nine children. ADHD is highly familial, and significant genetic underpinnings involve a cluster of common Single Nucleotide Polymorphisms (SNPs) that affect the metabolism, transport, or absorption of vitamin coenzymes and mineral cofactors. These coenzymes and cofactors are essential for all neuronal methylation pathways and cellular homeostasis, yet the combination of SNPs and their impact on ADHD severity and symptoms are unique to each patient. The interplay between genetics, environmental stressors, and nutritional factors actuate the biochemical causes of ADHD. Understanding and addressing these interactions encompasses the true definition of nutrigenomic treatment.

Unlike stimulant therapy, which may resolve symptoms temporarily, nutrigenomic therapy addresses ADHD at its genetic, biochemical, and nutritional causes. The genetic variants that lead to inadequate nutrient absorption, transport, and metabolism cannot be corrected by diet alone. This is only achieved by providing the CNS methylation pathways with the pre-metabolized B vitamin coenzymes, mineral cofactors, and phospholipid omega 3s that, to varying degrees, may be chronically suboptimal in the CNS of the ADHD patient. This study reports the results of an open-label trial evaluating coenzyme/cofactor monotherapy in pediatric ADHD. The two preparations used were gel cap or gummy forms. We utilized the brand "EnLyte," as both forms contained identical formulations of all essential B vitamin coenzymes, mineral cofactors, omega-3, and omega-6 fatty acids, required by the CNS for optimal methylation, monoamine production, membrane integrity, synaptic transmission, and antioxidant protection.

All 38 study completers (ages ranged from 2 to 13) responded well to coenzyme/cofactor therapy, with a mean reduction in the Conner's' Parent Rating Scale from 54.7 to 29.6 after 90 days of therapy. There were no discontinuations due to side effects. Further, there were no "non-responders" in the sample, as each patient demonstrated some degree of benefit, even when compliance was less than 100%. These results suggest that coenzyme/cofactor therapy is a well-tolerated nutrigenomic strategy for pediatric ADHD, and larger placebo-controlled trials are warranted.

Keywords: ADHD, MTHFR, Coenzyme, Cofactor, Nutrigenomic, B12, Folate, SNP, Essential minerals, Omega-threes

Introduction

Attention deficit hyperactivity disorder affects at least 11.4% of U.S. children, with approximately 60% of cases categorized as "moderate or severe" [1]. The American Academy of Pediatrics and CDC recommendations emphasize the recognition and treatment of ADHD in pre-school children for the mitigation of "social, emotional and academic problems" [2]. Non-pharmacological therapy and behavioral interventions are recommended as first-line for ages 2 through 6, yet over 68% of pre-school children with ADHD have been prescribed medication prior to age seven [3]. Further recent data showed a 20.4% increase in stimulant prescriptions for these patients from 2019 to 2023 [4].

Though clinicians and parents may be aware of the effectiveness and safety of integrative and functional therapies for ADHD in the pediatric population, many are unsure of which agent, or combination of ingredients to recommend. Specifically, regarding nutrient-based coenzyme and cofactor ingredients, they may be further confused by the wide range of commercially available doses and forms, and unsure of which preparations are optimal for transport and CNS utilization. This open label trial included patients ranging from 2 to 13 years of age, whose ADHD symptoms responded robustly to EnLyte monotherapy in gummy or gel cap form. EnLyte products are designed to target the complete genomic deficiencies associated with impaired methylation in the ADHD patient. By providing the essential B vitamin coenzymes, mineral cofactors, and plant-based omega 3s, 6s, and 9s, and in necessary proportions, normalization and balancing of chronically impaired methylation pathways can occur. The result is that biochemical end products necessary for clinical response, such as S-Adenosyl-Methionine (SAMe), neurotransmitters, glutathione and taurine, are adequately synthesized. Further, EnLyte Gummies and gel caps were designed to contain the most bioactive "end point metabolite" forms of each ingredient [5]. Each patient received genomic testing prior to beginning the 90-day trial, and 38 of 41 subjects were adequately compliant with Enlyte Gummies or gel caps taken once daily. All the compliant patients achieved some degree of response, and of the 38 completers, the average Conner's' Parent Rating Scale (Conners 3-P) score declined from 54.7 to 29.6 by study end. No patient discontinued therapy due to a reported side effect, and no adverse events were attributable to Enlyte therapy of either form. Seven cases (from ages 2 to 11) of the 38 study completers are detailed in the case series below.

Methodology

Patients aged 2 to 13 were screened for inclusion, the majority of whom had previous rating scales and/or neuropsychological assessments confirming ADHD. Those new to the clinic were assessed with patient and parent interviews, and all received the Conners' Parent Rating Scale (Conners 3) at entry. Also, each participant received genetic profiling utilizing the MaxGen panel (described at www.maxgenlabs.com). Exclusion criteria included active mood disorders of a severity requiring medication, or that impaired functioning, or any condition that prevented routine activities such as school or preschool attendance. All received Enlyte Gummy or EnLyte gel cap therapy, dosed at one daily. Biweekly evaluations continued for the 90-day duration of the trial, and at study end, a final Conners 3 scale was administered.

Specifically, Enlyte Gummy contains l-methyl folate magnesium 1.7 mg, methyl cobalamin (B12)16.7 mcg, (pyridoxine hydrochloride (B6) 16.7 mcg, thiamine HCl (B1) 8.3 mcg, riboflavin (B2) 8.3 mcg, nicotinamide adenine dinucleotide 8.3 mcg, DHA/EPA Omega Ahiflower Algal Oil Blend 2.7 mg, phospholipid (phosphatidylserine) 25 mg, magnesium citrate 16.7 mg, and zinc citrate 6.7 mg. The Enlyte formulations are all-natural, and free of gluten, wheat, dairy, and all sugars. They contain no dyes or artificial flavors and are described by the manufacturer as a "methylation coenzyme/cofactor/omega 3/6 broad-spectrum agents in gel cap or gummy forms" [5].

Results

Of the 41 patients entered, 38 were study completers, while 3 were noncompliant from an early date. Eleven were 100% compliant, 17 patients were greater than 75% compliant, and the remaining 10 were at least 50% compliant with EnLyte Gummies or gel caps. The mean Conners score at entry was 54.7, and at study end, three months later, the mean score for study completers was 29.6. Of note, the patients with at least 75% compliance Conners scores at study end were not statistically separated from the patients with full compliance. Figure 1 compares Conners 3 scores from the start to the end of the study. Genetic profiles were consistent with prior ADHD trials, with Methylenetetrahydrofolate Reductase (MTHFR) polymorphism being the most frequent variant noted.

The prevalence of MTHFR CT heterozygous was 40% of patients, and 10% were homozygous. The rate of MTHFR AC 50% heterozygous and 10% homozygous, while MTHFR GA was 24%. Approximately 20% were noted to have MTHFR compound heterozygosity. Figure 2 lists the occurrence of other genetic variants associated with ADHD in our study population, including Catechol-O-Methyltransferase (COMT H62H, L136L, and V158M), Diamine Oxidase (DAOI (AOC1), (AOC1)2, and (AOC1)3), D-Amino Acid Oxidase Activator and D-Amino Acid Oxidase (DAOA-DAAO), Dihydrofolate Reductase (DHFR), Dehydrogenase/Reductase 2 (DHR2), Dopamine Receptor D2 (DRD2), the Interleukin family (IL-1B, IL-6, IL-6R, IL-8), Monoamine Oxidase A (MAOA R27R and T1410C) and Monoamine Oxidase B (MOAB).

Case series

Case 1: AB is an 11-year-old who presented with psychological testing confirming ADHD and she had consistently performed below grade level in all subjects, particularly math and reading. Teachers reported focusing issues, inability to complete tasks and assignments, and that many assignments that she completed were simply not turned in. Teachers also noted that exposure to material was not correlated with recall, as she was often described as "tuning out" during class. Her Conners score was 45 at the start of therapy. Her genetic profile included MTHFR positive status (A1298C heterozygous), fast MAO and slow COMT activity, and a moderate reduction in DAO activity.

AB complied with EnLyte (ENL) gelcap therapy, taking one gelcap daily for 90 days (missing only one dose). At the study's conclusion,

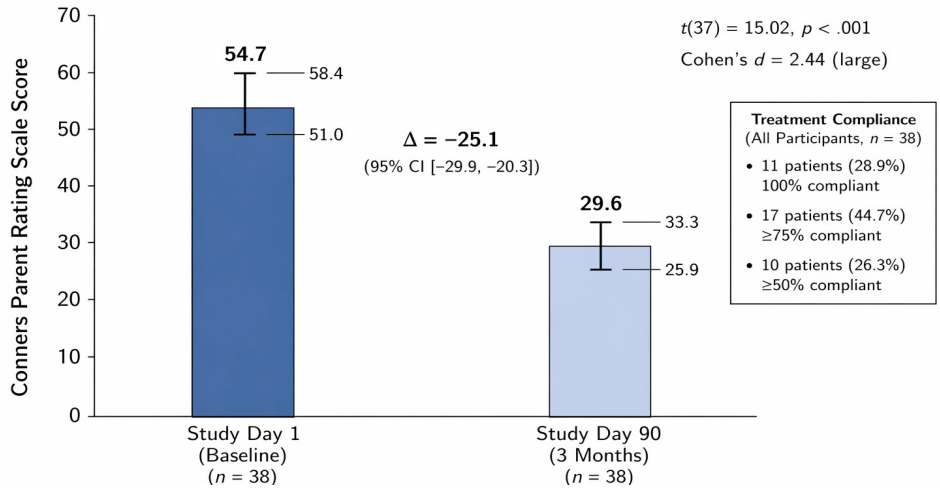

Figure 1 Conners parents rating scale at study day one and day 90 (3 months) including participants.

Note: Bars represent mean scores with error bars indicating ± 3.7 points (means deviation) above and below the mean. Scores range from 0 to 100. with higher scores indicating greater symptom severity. all participants (N=38) are included in the analysis.

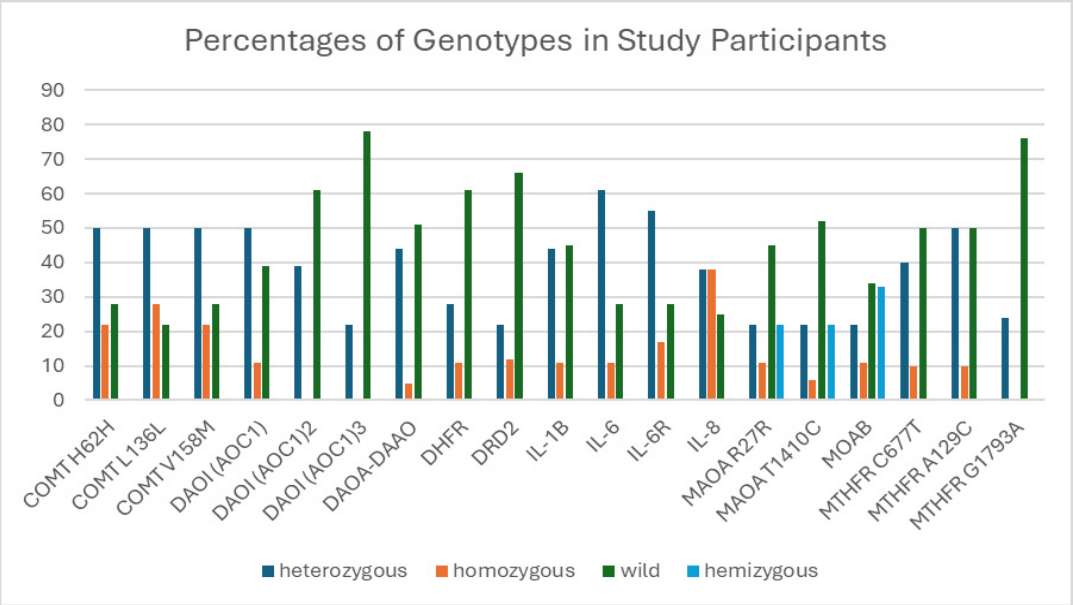

Figure 2 Prevalence in percentages of the SNPs and polymorphisms in our ADHD study population, involving: COMT H62H — *Catechol-O-methyltransferase* (histidine at codon 62, synonymous variant), COMT L136L — *Catechol-O-methyltransferase* (leucine at codon 136, synonymous variant), COMT V158M — *Catechol-O-methyltransferase* (valine → methionine substitution at codon 158), DAO1 (AOC1) — *Diamine Oxidase 1* (also called *Amine Oxidase, Copper Containing 1*) DAO1 (AOC1)2 — Variant in *Diamine Oxidase*, DAO1 (AOC1)3 — Variant in *Diamine Oxidase*, DAOA–DAAO —*D-amino acid oxidase activator* (also called G72), DHFR — *Dihydrofolate reductase*, DRD2 — *Dopamine receptor D2*, IL-1B — *Interleukin 1 beta*, IL-6 — *Interleukin 6*, IL-6R — *Interleukin 6 receptor*, IL-8 — *Interleukin 8* (also known as CXCL8), MAOA R27R — *Monoamine oxidase A* (arginine at codon 27, synonymous variant),

MAOA T1410C — *Monoamine oxidase A* (thymine → cytosine substitution at position 1410), MAOB — *Monoamine oxidase B*, MTHFR C677T — *Methylenetetrahydrofolate reductase* (cytosine → thymine at position 677), MTHFR A129C — *Methylenetetrahydrofolate reductase* (likely refers to A1298C: adenine → cytosine at position 1298), MTHFR G1793A — *Methylenetetrahydrofolate reductase* (guanine → adenine at position 1793)

teacher reports indicated she was "much more attentive in class and has been able to complete most assignments during class time." Her recall of material was improved and reflected in higher grades. Parents were pleased that she would now "do homework right away when arriving home." Her Conners score at the end of the study was 22. She remains on EnLyte five months post study and is current in performance with her grade level in all subjects with report cards noting a "confidence that is rebuilt."

Case 2: BC is a 3-year-old male who was described as "fully or partially" inattentive to instructions from parents and teachers.

When he was asked to do routine chores or activities (dressing, brushing teeth), the request was usually met with emotional dysregulation (principally anger outburst). He was unable to remain still if an activity was not of interest and engaging him in continual activity. His Conners 3 score at the start of EnLyte Gummy therapy was 55. His Genetic SNPs included: MTHFR (A1298C heterozygous status), very slow MAO enzymatic activity, and very fast COMT activity. BC complied with EnLyte Gummy 75% of the 90 days. At study end, he was described by teachers as "now able to follow directions for preschool activities, and his outburst were no longer an issue." His Conners score at study's end was 27.

Case 3: CD is an 11-year-old male noted to be very easily distracted, and parents and teachers confirmed he "always requiring instructions be repeated many times." The patient himself acknowledged his mind "always jumped around" and he described doing homework and studying as "impossible." His grades were below passing in most subjects, and his Conners score was 51.

He was noted to be MTHFR negative, while other SNPs resulted in very fast MAO activity, with a minimal decrease in DAO activity. His compliance was measured at 75% of prescribed doses of EnLyte (ENL) gelcap. At the 90-day period, teachers noted increased attention during lectures, improved focus, and fuller comprehension of instructions. Nighttime anxiety had also dissipated as the patient reported no longer dreading the next school day. His Conners score at day 90 was reduced to 25.

Case 4: DE is a 7-year-old female whose principal symptoms included distractibility (especially in group settings), "tuning out" instructions, and always needing repetition even for simple tasks. Parents reported she was "terrible at expressing feelings with words and will often just remove herself or will get angry." Her Conners score at the start of the trial was 48. DE's genetic profile included MTHFR (C677T heterozygous status), slow COMT and MAO activity, and mildly compromised DAO activity. DE was fully compliant with one EnLyte Gummy daily and at the end of the study she was greatly improved at staying focused on tasks. According to parents, she was also "much less emotionally volatile," and was better able to express her frustrations and articulate her feelings. She was no longer leaving her seat during class, meals, or in other situations in which remaining seated was expected. Her Conners had reduced to a score of 21.

Case 5: EF is a 10-year-old male who had performed below grade levels since beginning elementary school. He reported great difficulty concentrating, which led him to a sense of frustration as well an awareness of the incompleteness in his work. Teachers noted this was why he had such anxiety when asked to shift from one assignment to another and had difficulty stopping any task. In a competitive school where he felt inadequate, his self-esteem suffered. His own chief complaint on mental status exam at study entry was "I have no friends." His Conners 3 score was 46 at study initiation. EF was MTHFR positive (C677T heterozygous) with other SNPs indicating low COMT and very fast MAO activity. His compliance with ENL gelcap was 75% of doses. By the end of the study, reports indicated improved focus at home and in class. Teachers were "pleased and surprised" by the changes, and the patient himself stated he "doesn't feel like he gets as emotional as he did before" and elaborated he is "better at having friendships." At the start of the study an antidepressant was considered, but as EnLyte (ENL) gelcap therapy progressed, it was deemed unnecessary. His Conners 3 score was 21 by day 90.

Case 6: FG is a 2 -year-old male who was inattentive to his surroundings and with the slightest distraction would walk or run into furniture or other objects. Teachers indicated he was usually "sidetracked while following one simple direction" when he saw anything that caught his attention. Though young, his attentiveness was more compromised than would be age appropriate. However, his developmental milestones were on track, and psychological testing did not indicate any issues with his IQ. Genetic SNPs included a positive MTHFR status (A1298C homozygous), slower than normal MAO activity, and a moderate decrease in DAO activity. FG was fully compliant with a daily EnLyte Gummy. By the end of study, he was able to follow one-step, and usually two-step, instructions, and was more attentive and able to respond to questions. His routine mobility posed no unusual risk due to inattentiveness to surroundings. He was potty trained during this time, as he was better able to focus during this period.

Case 7: GH is an 11-year-old female who self-reported an inability to remember instructions given in class. She further described herself as in a "brain fog," especially during lectures or hearing teachers advise her and correct her assignments. She also identified herself as "always emotionally over-reactive," even at "the smallest things." [BA34.1][BF34.2] She noted her tendency to be obsessive about her own "internal plans and timeline," but was unable to communicate this to teachers and adults and reported she would "melt down" when her internal expectations are disrupted. She is noted to rush through all activities and feel incapable of doing work slowly or meticulously. She often left tasks and assignments nearly complete. Conner was scored at 40 at the start of therapy. OCD therapy was also considered, but the decision was mutually made to see what improvement may occur with EnLyte Gummy monotherapy.

Her genetic testing confirmed MTHFR positive status, compound heterozygous for C677T and A1298C, slow COMT, and a severe reduction in DAO activity. GH complied fully with her EnLyte Gummy for the 90-day study. By the end, she stated she was now better able to cope with routine experiences that "once made her nervous." Previously routine assignments and activities were the source of excessive anxiety and she often required lengthy interventions to prevent "melt downs." She demonstrated much more self-control and believed her "thoughts work slower" and no longer "overreacts." She now often completed chores without being asked. Conners improved to 16, and her Y-BOCS score dropped from 41 to 20 during the same time [6-24].

Discussion

ADHD's genetic basis

ADHD is a highly heritable and polygenetic condition with studies estimating heritability at 80-90%. A recent meta-analysis study

of genes associated with ADHD identified 27 significant loci, and highlighted 76 potential risk genes that were enriched, particularly among those expressed in early brain development. This analysis confirmed that ADHD is influenced by thousands of variants, the vast majority of which were also noted to influence other psychiatric disorders [6]. Of the numerous SNPs and genetic variants, the ones associated with both causality and symptom presentation that can be addressed nutrigenomically are: MTHFR, methylenetetrahydrofolate dehydrogenase 1 (MTHFD1), Diamine Oxidase (DAO), Transcobalamin II (TCN2), Monoamine Oxidase A (MAO-A), serine hydroxymethyltransferase (SHMT), Betaine–Homocysteine S-Methyltransferase (BHMT), Dihydrofolate Reductase (DHFR), Catechol-O-Methyltransferase) (COMT), and Adenosylhomocysteinase (AHCY).

The A1298C form of the MTHFR variants is consistently reported at higher frequencies in ADHD patients [7]. And some studies correlate the C677T polymorphism with increased symptom severity [8]. MTHFR variants reduce the body's ability to convert folic acid or dietary folate to l-methylfolate. This final product of the folate cycle is necessary for one-carbon metabolism, neurotransmitter synthesis, and methylation of numerous compounds and moieties.

In addressing these MTHFR and other folate-related SNPs, methylated folate, methyl-cobalamin and pyridoxal-5-phosphate (the essential coenzyme form of vitamin B6) are all necessary in order to restore optimal methylation. Further, because only B12 bound to transcobalamin (holotranscobalamin) can enter cells via the CD320 receptor, TCN2 mutations will affect methylation substantially by limiting cellular delivery of B12, essential for the folate-dependent methylation cycle.

The DAO enzyme degrades extracellular histamine (and other diamines), primarily in the gastrointestinal system, thus, its activity influences systemic histamine levels.11 Thus, DAO variants are also expected to influence gut-brain inflammatory pathways that modulate the comorbidity burden associated with ADHD, as well as directly impacting cognitive acuity and irritability [9,10]. COMT variants (especially Val158Met) are widely studied in ADHD populations, as they impact prefrontal dopamine levels, key for executive functioning [11]. COMT SNPs are also linked to levels of hyperactivity and impulsivity in ADHD [12], while MAO variants influence general monoamine breakdown. Evidence suggests that MAO alterations are also potentially linked to impulsivity, and emotional and behavioral dysregulation [13].

Aadenosylhomocysteinase SNPs can significantly impact methylation capacity because of their central role in the one-carbon cycle. AHCY prevents accumulation of S-adenosylhomocysteine (SAH), a potent inhibitor of methyltransferases. It is also responsible for maintaining the critical SAM:SAH ratio, which determines cellular methylation capacity. Even for patients with adequate methyl-folate, methlycobalamin, and normal SAM levels, AHCY SNPs can still cause functional methylation deficits, because SAH accumulation directly blocks methyltransferases [14]

Betaine–homocysteine S-methyltransferase SNPs that influence methylation will likely contribute to ADHD symptoms. The BHMT enzyme provides a folate-independent pathway to remethylate homocysteine into methionine, supporting SAM (S-adenosylmethionine) production and methylation. It is active primarily in the liver and kidney, yet peripheral methylation can influence the CNS via methyl donors. The effects of these SNPs are usually inconsequential if alone, but when combined SNPs, and low methyl donor nutrients, their impact is more significant on methylation and ADHD-related pathways [15].

Theory into practice

Multiple previous studies have established that "mineral-vitamin" therapy, sometimes referred to as "broad spectrum micronutrient therapy," demonstrate global benefit compared to placebo in ADHD trials of pediatric patients [16,17]. Metabolized B vitamins are coenzymes in countless reactions, and mineral cofactors are involved in at least a third of all proteins requiring a metal ion to function. Mineral cofactors are often structural components, enabling protein stability. The majority of micronutrient studies were conducted prior to the first complete, gapless human genome mapping, that informed all DNA base pairs (over 3 billion) which included at least 4 million SNPs [18]. We now have the opportunity to evolve ADHD therapy to a standard that targets a plethora of common methylation genetic variants, many of which correlate with symptoms presence and severity. By providing the CNS with optimal levels of coenzymes and cofactors, in the forms of fully metabolized vitamins and necessary minerals, the EnLyte Gummy or gel cap forms address methylation SNPs that current drug stimulant therapies cannot.

The strategy may also address certain genetic variants that compromise enzyme structure and functioning, as the presence of supra-optimal coenzymes and mineral nutrients has been shown to enhance the activity of the less functional enzymes they serve. For example, in some patients, especially those with milder mutations or partial defects, high-dose B12 and folate supplementation has been used to maximize inadequate methionine synthase activity [19]. EnLyte formulations eliminate the uncertainty of exactly which combination of natural therapies to recommend, in what doses, and in what forms. In children as young as 2 years of age, EnLyte was well tolerated, with only one patient reporting some agitation which resolved by lowering the dose to every other day. In the taste portion part of the study, 72.4% of children surveyed reported they liked the taste of the gummy form [20].

When compliance dropped to 75% in this open label trial, response was still robust by study end, and consistent with the mean response of the group that was fully compliant. The responses seen with at least 50% compliance was less than the two more complaint groups, their average Conners 3 score being 5.1 points higher at study end, yet all still qualified as responders.

These improvements with less than full compliance argue that nutrigenomic therapy resolves symptoms via ongoing dietary management and restoration of neuronal homeostasis. While stimulant therapy may temporarily improve symptoms, it cannot address causative physiology, nor the chronic nutritional compromises associated with ADHD.

Comorbidities, such as OCD in patient GH, and depressive symptoms in patient EF, also improved as ADHD symptoms decreased in severity. According to the Centers for Disease

Control and Prevention (CDC), 77.9% of U.S. children with ADHD had at least one co-occurring psychiatric or developmental condition [21]. In a prior trial of EnLyte for pediatric depression, in which some patients required traditional stimulants for ADHD, they were noted to further improve regarding emotional dysregulation and other comorbidities with the addition of EnLyte [22].

Further, comprehensive nutrigenomic therapy may not only ameliorate or resolve symptoms as evidenced in this study, but offers patients future disease prevention through neuroprotection, facilitates CNS structural development, as well as genomic protection and repair, again, by providing adequate methylation and redox stability. In addition, L-methylfolate and/or L-leucovorin can help facilitate optimal CSF folate absorption to address Cerebral Folate Deficiency, which is common in the ADHD population, as well autism spectrum disorder [23]. EnLyte gelcaps are also indicated for the dietary management of major depressive disorder (MDD), particularly for individuals with MTHFR SNPs or other methylation-related cofactor deficiencies. Enlyte was shown in a 330-patient placebo-controlled trial, to significantly reduce plasma homocysteine levels while achieving an average 42% remission in depressive symptoms with a 0.93 effect size in adult patients with MTHFR positive for MDD. Patients experienced a 33% reduction in homocysteine levels and on average compared to a slight increase in the placebo group, and a 12 point decrease on the MADRS scale, compared to placebo, with no significant increase in side effects versus placebo [24].

Conclusion

The EnLyte preparations chosen for our open label trial were designed to offer the pediatric ADHD patient the most bioavailable forms of coenzymes and cofactors. They are FDA regulated “Medical Foods” and indicated for the dietary management of ADHD or Depression with no age restrictions. EnLyte formulations are designed to address all potential methylation-based and root because genetic vulnerabilities, as well as dietary deficiencies associated with ADHD risk, symptom presence, and symptom severity. There were no “non-responders” and seven who were deemed partial responders did eventually further benefit from the addition of stimulant medications, all of whom benefited at doses lower than previous needed, or lower than standard doses.

Of particular importance is addressing the age 2 to 6 treatment void with evidence based, all natural, and effective nutrigenomic therapy. The gummy and gel cap forms were also designed with the pediatric patient in mind. We argue that the future of ADHD therapy in our pediatric population should begin with coenzyme/cofactor therapies that target the underlying causes and environmental contributors to the condition. Traditional stimulant medicine may be adjunctive and helpful in many cases, yet the platform of nutrigenomics agents may lower the dosage threshold needed for response.

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