Outcome-Based Comparison of Ritalin® versus Food-Supplement Treated Children with AD/HD

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Abstract

Twenty children with attention deficit/hyperactivity disorder (AD/HD) were treated with either Ritalin™ (10 children) or dietary supplements (10 children), and outcomes were compared using the Intermediate Visual and Auditory/Continuous Performance Test (IVA/CPT) and the WINKS two-way analysis of variance with repeated measures and with Tukey multiple comparisons. Subjects in both groups showed significant gains ($p \leq 0.01$) on the IVA/CPT's Full Scale Response Control Quotient and Full Scale Attention Control Quotient ($p \leq 0.001$). Improvements in the four sub-quotients of the IVA/CPT were also found to be significant and essentially identical in both groups: Auditory Response Control Quotient ($p \leq 0.001$), Visual Response Control Quotient ($p \leq 0.05$), Auditory Attention Quotient ($p \leq 0.001$), and Visual Attention Quotient ($p \leq 0.001$). Numerous studies suggest that biochemical heterogeneous etiologies for AD/HD cluster around at least eight risk factors: food and additive allergies, heavy metal toxicity and other environmental toxins, low-protein/high-carbohydrate diets, mineral imbalances, essential fatty acid and phospholipid deficiencies, amino acid deficiencies, thyroid disorders, and B-vitamin deficiencies. The dietary supplements used were a mix of vitamins, minerals, phytonutrients, amino acids, essential fatty acids, phospholipids, and probiotics that attempted to address the AD/HD biochemical risk factors. These findings support the effectiveness of food supplement treatment in improving attention and self-control in children with AD/HD and suggest food supplement treatment of AD/HD may be of equal efficacy to Ritalin treatment.
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Introduction

Attention deficit/hyperactivity disorder (AD/HD) is classified by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) as a mental disorder primarily characterized by a "persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development." The DSM IV explicitly defines the meaning of the term "disorder."[1]

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"In DSM-IV, each of the mental disorders is conceptualized as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important areas of functioning).... Whatever its original cause, it must currently be considered a manifestation of a behavioral, psychological, or biological dysfunction in the individual.... In DSM-IV, there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder. There is also no assumption that all individuals described as having the same mental disorder are alike in all important ways. The clinician using the DSM-IV should therefore consider that... individuals sharing a diagnosis are likely to be heterogeneous even in regard to the defining features of the diagnosis and that boundary cases will be difficult to diagnose in any but a probabilistic fashion."

Although individuals diagnosed with AD/HD share a similar range of outward behavioral symptoms, the underlying causalities are "likely to be heterogeneous,"[2] a term defined as "of unlike natures, composed of unlike substances" and "consisting of dissimilar or diverse ingredients or constituents."[3] Such heterogeneity could be within biological, psychological, and/or social levels of organization (The Biopsychosocial Model)[4] or could vary widely within each level of organization for each individual with AD/HD. At least at the biological level of the biopsychosocial model, an extensive literature review by Kidd strongly supports a heterogeneous molecular etiology for AD/HD, with each individual likely to have a unique array of abnormalities expressed symptomatically as AD/HD.[5]

There is a complex body of information suggesting multiple, heterogeneous, biochemical etiologies for AD/HD. For purposes of discussion and clinical utility, the information can be assembled into eight general etiological categories: (1) food and additive allergies;[6-25] (2) heavy metal toxicity and other environmental toxins;[26-36] (3) low-protein, high-carbohydrate diets;[37-39] (4) mineral imbalances;[40-52] (5) essential fatty acid (EFA) and phospholipid deficiencies;[53-57] (6) amino acid deficiencies;[58-63] (7) thyroid disorders;[64-67] and (8) B-vitamin and phytonutrient deficiencies.[68-74]

Each of the publications noted above examines only the relationship of AD/HD to a single or a few risk factors. Furthermore, within each etiological category, the studies primarily examine only the relationship of AD/HD to a single or a few variables within each category. Exemplary variables included, but were not limited to, various food and additive allergies, two toxic metals (aluminum and lead), several B-vitamin (B1, B3, and B6) deficiencies, several amino acid (tryptophan, tyrosine, and D- and L-phenylalanine) deficiencies, thyroid abnormalities, a high-carbohydrate and low-protein diet, endogenous protein and carbohydrate metabolic abnormalities, EFA deficiencies of the omega-3 series, and abnormalities in several essential minerals (iron, selenium, zinc, copper, phosphorus, calcium, and magnesium).

The neurobiological etiology of AD/HD has been postulated to be associated with deficiencies in catecholamines, such as norepinephrine and dopamine,[75] with little discussion concerning the physiological origins of the multifaceted mechanisms required to generate such neurotransmitters. Likewise, the therapeutic effect of Ritalin® is thought to be linked to its effects on norepinephrine and dopamine.[76] In contrast to this view of neurotransmitters as isolated variables that exist independent of the whole organism, this study protocol attempted to restore and regulate neurotransmitters in test subjects by supplementing the diet with amino acid precursors (e.g., tyrosine) likely to be deficient in the subject as determined by symptoms. For instance, since tyrosine is the precursor for dopamine and norepinephrine, and deficiencies in these excitatory neurotransmitters are likely to be a factor in inattentiveness, subjects who displayed predominantly inattentive symptoms (as opposed to hyperactivity) were provided with extra tyrosine as part of their supplement regimen. In addition, vitamin and mineral co-factors for neurotransmitter formation were supplemented. Other etiological factors were addressed by nutrients as indicated.

Table 1a. *Supplements Used in the Alternative Treatment Group*

Gastrointestinal and Immune Support (Risk Factor #1)
(1) Lactobacillus acidophilus and bifidus
(2) Lactoferrin (5 mg)
(3) Silymarin (5 mg)

Sulfur-Containing Supplements and Glycine (Risk Factor #2)
(1) Taurine (275-425 mg)
(2) Glycine (700-1830 mg)
(3) Methionine (25-75 mg)
(4) N-acetylcysteine (NAC) (0-10 mg)
(5) L-cysteine (0-25 mg)
(6) Glutathione (20 mg)
(7) alpha Lipoic acid (5 mg)
(8) Garlic extract (200 mg)

Amino Acids (Risk Factors #3 and #6)
(1) Tyrosine (900-1800 mg)
(2) Histidine (25-75 mg)
(3) Glutamine (600-1400 mg)
(4) alpha Ketoglutarate (AKG) (25-75 mg)
(5) L-carnitine (30 mg)

Minerals (Risk Factor #4)
(1) Magnesium (as magnesium glycinate) (220-480 mg)
(2) Calcium (as calcium ascorbate) (110-170 mg)
(3) Potassium (as glycerol phosphate) (46-70 mg)
(4) Chromium (as nicotinate) (140-200 mcg)
(5) Selenium (as methionate) (26-32 mcg)
(6) Zinc (as monomethionate) (9-15 mg)
(7) Manganese (as arginate) (2.5-4 mg)
(8) Boron (as citrate) (1200-1800 mcg)
(9) Copper (as tyrosinate) (1.2-2.4 mg)
(10) Silica (4 mg)
(11) Molybdenum (as chelate) (5-40 mcg)
(12) Vanadium (chelate) (2-20 mcg)
(13) Iron (as glycinate) (1-2 mg)

acids (Table 1a and 1b). The dietary supplements chosen were those most likely to address the eight etiological factors previously noted and as outlined by Gant.[77] All children in the Ritalin group received prescribed doses of 5-15 mg Ritalin 2-3 times daily, as determined by the prescribing physician.

To be eligible, children had to be 7-12 years old, and were required to be without any other medication or treatment, street drugs, or other nutritional or botanical supplements. The psychologist screened patients to rule out co-morbid disorders. These criteria were selected because previous studies of specific treatment for AD/HD children encouraged diagnostic heterogeneity (not molecular or biological heterogeneity) to reduce factors that may affect treatment response.[78] For example, children found to have co-existing conduct disorder or oppositional defiant disorder were screened out of this study.

Patients and Methods

Twenty children diagnosed with AD/HD by a clinical child psychologist were divided into two groups by parental choice. Ten subjects were prescribed Ritalin by a family physician. The other 10 were prescribed dietary supplements by a certified nurse clinical specialist. Supplementation consisted of a multiple vitamin, a multiple mineral, phytonutrients, essential fatty acids and phospholipids (soy lecithin), probiotics, and amino

Subsequent to diagnostic screening, parents were given literature regarding AD/HD, information about conventional drug treatment (Ritalin), and a booklet describing unconventional (alternative) treatments with dietary supplements. Parents who chose Ritalin were referred back to their family physicians to acquire a prescription, while parents who chose dietary supplement treatment were referred to a psychiatric nurse clinical specialist for counseling regarding types, amounts,

and frequency of administration of supplements. Parents were also informed and signed a consent form to allow the data to be included in a doctoral dissertation for a clinical psychology program.

Diagnostic methods included a developmental history, an assessment of DSM-IV diagnostic criteria,[1] the Conner's Parent Rating Scale (1989-1990),[79] and the Intermediate Visual and Auditory/Continuous Performance Test (IVA/CPT).[80] The Conner's Parent Rating Scale – Revised: Long Form (CPRS-R:L) was developed to assess a wide range of childhood behavioral difficulties, including conduct disorders, problems of cognition, social difficulties, and anxiety. The revised version has achieved excellent reliability and validity.

The IVA/CPT has high reliability and validity in diagnosing and assessing AD/HD treatment efficacy as well as medication titration. The IVA/CPT is a computerized, standardized test developed for the assessment of response inhibition and attention problems. This test is characteristically unique because it tests for auditory as well as visual distractibility. The test analysis yields detailed reports on 22 different scales. The six primary composite quotient scales

are: (1) prudence, in which the subject thinks before acting and avoids impulsive errors of commission; (2) consistency, in which most of the subject's response times are clustered within a narrow range; (3) stamina, which is the subject's response times as maintained for the duration of the test; (4) vigilance, in which the subject identifies all targets by avoiding inattentive errors of commission; (5) focus, in which the subject shows no evidence of momentary lapses; and (6) speed, in which the subject response times are rapid, providing evidence that the brain's resources are dedicated to the task at hand. The quotient

Table 1b. *Supplements Used in the Alternative Treatment Group*

Essential Fatty Acids and Phospholipids (Risk Factor #5)
(1) Salmon oil 1000 mg (EPA 180 mg; DHA 120 mg)
(2) Borage oil 200 mg (GLA 45 mg)
(3) Purified Soy Lecithin (Phosphatidyl choline 50-150 mg; Inositol 20-25 mg)
(4) Choline bitartrate (2.5-7.5 mg)

Agents to Support Thyroid Functioning (Risk Factor #7)
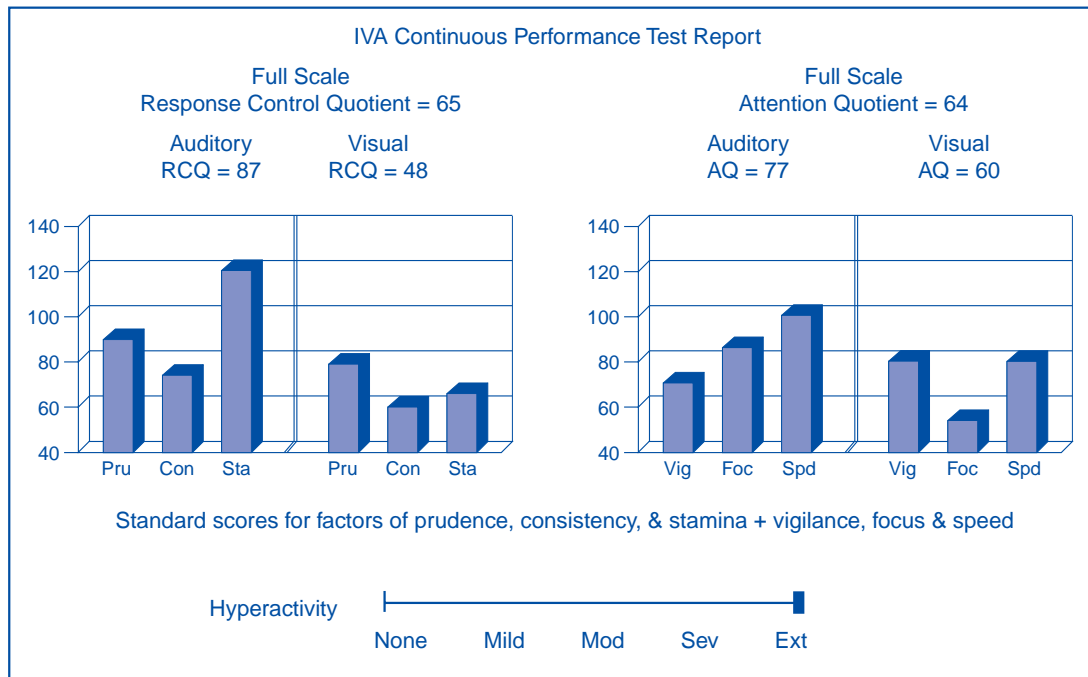(1) Iodine (from kelp) (25-150 mcg)
(2) Tyrosine (900-1800 mg)

B Vitamins and Phytonutrients (Risk Factor #8)
(1) Vitamin B1 (as thiamine and thiamine pyrophosphate) (22.5-27.5 mg)
(2) Vitamin B2 (as riboflavin and riboflavin phosphate) (22.5-27.5 mg)
(3) Vitamin B3 (as niacin and niacinamide) (75-140 mg)
(4) Vitamin B5 (as D-calcium pantothenate and pantethine) (50-70 mg)
(5) Vitamin B6 (as pyridoxine and pyridoxal-5-phosphate) (43-86 mg)
(6) Vitamin B12 (cyanocobalamin) (90-175 mcg)
(7) Folic acid (435-760 mcg)
(8) Biotin (20-400 mcg)
(9) PABA (22.5-27.5 mg)
(10) Vitamin E (140-200 IU)
(11) Vitamin C (750-1000 mg)
(12) Vitamin A (as vitamin A and beta carotene) (2000-4500 IU)
(13) Vitamin D3 (40-100 IU)
(14) Vitamin K (20 mcg)
(15) Royal bee jelly (source of biopterin) (75-150 mg)
(16) Dimethyl glycine (10 mg)
(17) Citrus bioflavonoids (10-20 mg)
(18) Proanthocyanidins (grape seed) (5 mg)
(19) Bilberry extract (20 mg)
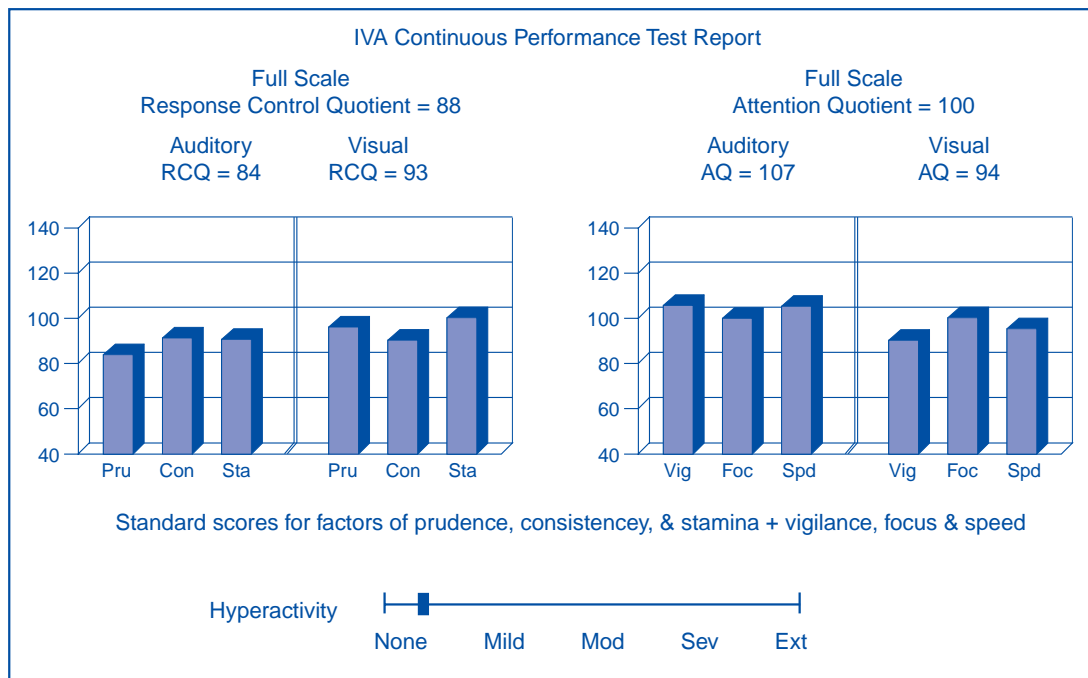(20) Soy constituents (saponins, isoflavones, phytosterols) (20 mg)

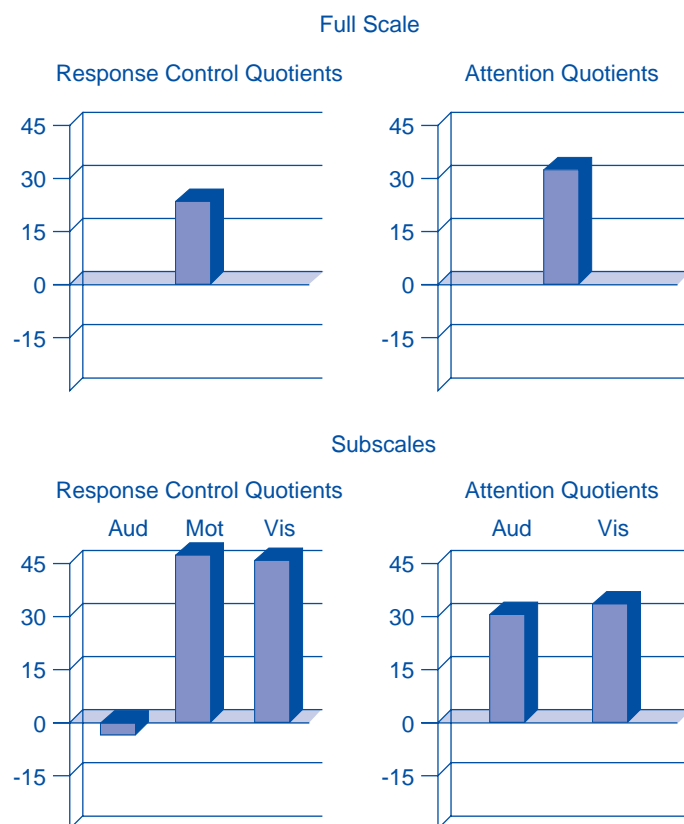***Figure 1.*** *Example of a Pre- and Post-treatment Test Report*

scores have a mean of 100 and a standard deviation of 15, the same as is utilized for most standardized IQ tests. The printed IVA/CPT results are presented in the form of graphs that allow comparisons to a normative sample and for test-retest evaluation. It is then possible to quickly compute the change in quotient scores between any two IVA/CPT tests in order to evaluate treatment effects.

Scores for the six primary scales of the IVA/CPT are obtained for both visual and auditory performance. There are two major quotients derived from these six scales. Prudence, consistency, and stamina comprise a Full Scale Response Control Quotient (FSRCQ), while vigilance, focus, and speed comprise a Full Scale Attention Control Quotient (FSACQ). These global composite quotient scales allow efficient summary and evaluation of the test results.

Statistical Analysis/Results

The primary outcome measure used was the IVA/CPT.[80] Figure 1 illustrates the results of pre- and post-treatment IVA/CPTs for a patient treated with nutritional supplements. Figure 2 "subtracts" the outcomes of the pre-treatment IVA/CPT from the post-treatment results and displays a net gain on both the FSRCQ, which measures impulsivity, and the FSACQ, which measure inattentiveness. Note these two global measurements of impulsivity and inattentiveness are further broken down into visual and auditory responses (i.e., visual inattentiveness versus auditory inattentiveness), and the FSRCQ has a third category of motor restlessness (fidgetiness) as well. Figure 1 further subdivides the IVA/CPT categories into "pru" (prudence), "con" (constancy), "sta" (stamina), "vig" (vigilance), "foc" (focus), and "spd" (speed).

Figure 2. *Example of an IVA/CPT Test Report Illustrating Pre-treatment Results Subtracted from Post-treatment Results*

In this completely computerized test, the participant responds to random auditory and visual cues from the computer. The cues are either the numbers 1 or 2, visually presented on the screen or auditorily via the speakers. The participant is instructed to only click the mouse when s/he hears or sees a 1 and to not click the mouse if s/he sees or hears a 2. The computer records mistakes (clicking on the 2 stimulus or not clicking on the 1 stimulus) and the time lags between the cued 1 stimulus and clicking the mouse. Individuals who have problems paying attention will have delays or misses when given the 1 stimulus. Individuals who are hyperactive will not be able to inhibit their impulses in a normal way when provided with a 2 stimulus. The test is standardized with controls matched by age and sex and correlates very well to more conventional AD/HD diagnostic testing. The computer prints scales (a score of 100 is average) for overall attention and impulse control (hyperactivity), and any score below 90 is one standard deviation from the norm. The computer then divides the two scales (attention and impulse control) into visual and auditory scales for each. These are further broken into subscales (focus, prudence, speed, etc.). Finally, the IVA/CPT compares multiple tests done on the same individual, subtracting previous performance from current results, so improvement or lack thereof can be measured accurately after treatment of AD/HD.

Comparison of the Ritalin treatment group and the group treated with dietary supplements was accomplished using a WINKS two-way analysis of variance with repeated measures as well as Tukey multiple comparisons.

The data was collected from the CPRS-R:L and IVA/CPT. The CPRS-R:L and IVA/CPT were both administered pre-treatment. The IVA/CPT was re-administered after four weeks of treatment for both groups. Retesting of the Ritalin group subjects was conducted two hours after their recommended dose, due to peak effect occurring within 1-3 hours. In contrast, no peak time was advised for the alternative treatment group. Subsequently, t-tests and tests for homogeneity of variance were used to analyze data on all sub-tests of the CPRS-R:L. Results of these analyses were used to evaluate equivalence or differences between groups. Statistical analysis used in assessing differences resulting from treatment within and between the dietary supplement and Ritalin groups was a two-way repeated measures analysis of variance for each of the scales of the IVA/CPT. Subsequent post-hoc comparisons were carried out where significant F ratios were found. The scores were compared by utilizing a WINKS two-way analysis of variance with Tukey WSD post-hoc comparison.[81]

The FSRCQ yielded significant pre-test to post-test differences for both the Ritalin and the alternative treatment groups (Figures 3 and 4). Subjects in both groups showed significant ($p \leq 0.01$) gains in the FSRCQ. Increases in FSACQ were also found to be significant ($p \leq 0.001$) for both the Ritalin and the alternative treatment groups (Figures 3 and 4). Comparative analyses indicated there were no significant differences in the level of improvement between the two groups. Thus, the effect of Ritalin versus dietary supplement treatment was found to be essentially the same, and both treatments were found to be effective after four weeks of use.

Increases in the four sub-scales or sub-quotients that comprise these two major scales were found to be significant as follows:
(1) Auditory Response Control Quotient (ARCQ ($p \leq 0.001$))
(2) Visual Response Control Quotient (VRCQ ($p \leq 0.05$))
(3) Auditory Attention Quotient (AAQ ($p \leq 0.001$))
(4) Visual Attention Quotient (VAQ ($p \leq 0.001$))

Post-hoc tests indicated homogeneity of variance for both groups on all sub-quotients and no significant between-group differences (Figures 3 and 4).

Discussion

This study compared outcomes of two distinct paradigms of AD/HD treatment – the pharmaceutical (Ritalin) and the nutraceutical (dietary supplements). Ritalin's therapeutic effect has been hypothesized to result from presynaptic dopamine transporter inhibition, thus increasing the availability of the neurotransmitter dopamine,[82] especially in the frontal lobes of the cerebral cortex.[83] Dietary supplements used in this study also potentially increase catecholamine(dopamine, norepinephrine, and epinephrine) synthesis by precursor loading (tyrosine is the precursor to dopamine and norepinephrine[84]) and delivering B-vitamin (vitamins B3, B6, and folic acid) and mineral (iron and copper) cofactors. Vitamin C is also a cofactor for the synthesis of the neurotransmitter norepinephrine, imbalances of which are also linked to AD/HD,[82] and may be beneficial in reducing toxicity of some heavy metals, such as lead. Phospholipids and essential fatty acids are necessary for cell membrane repair, especially in the developing central nervous system, and may improve synaptic physiology and neurotransmitter efficiency.[85] These essential lipids have also been utilized for gut enterocyte repair, which, along with reinnoculation of friendly flora and the administration of probiotics, could mitigate food allergy. Formal allergy testing, desensitization procedures, or rotation/elimination of potentially allergenic foods were not done in this study.

Figure 3. IVA/CPT Pre- and Post-treatment Mean Scores for the Alternative Treatment Group
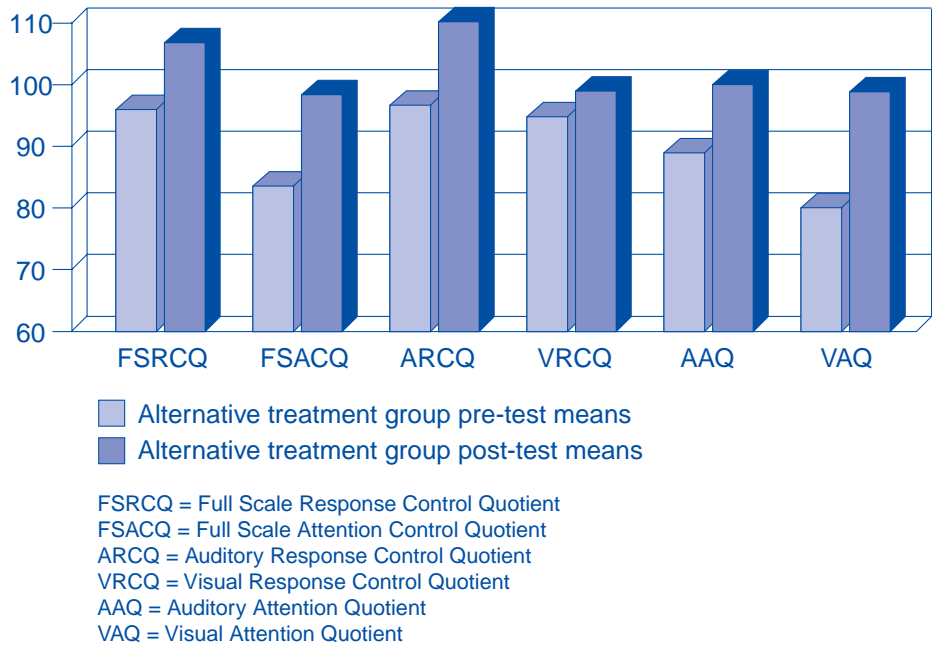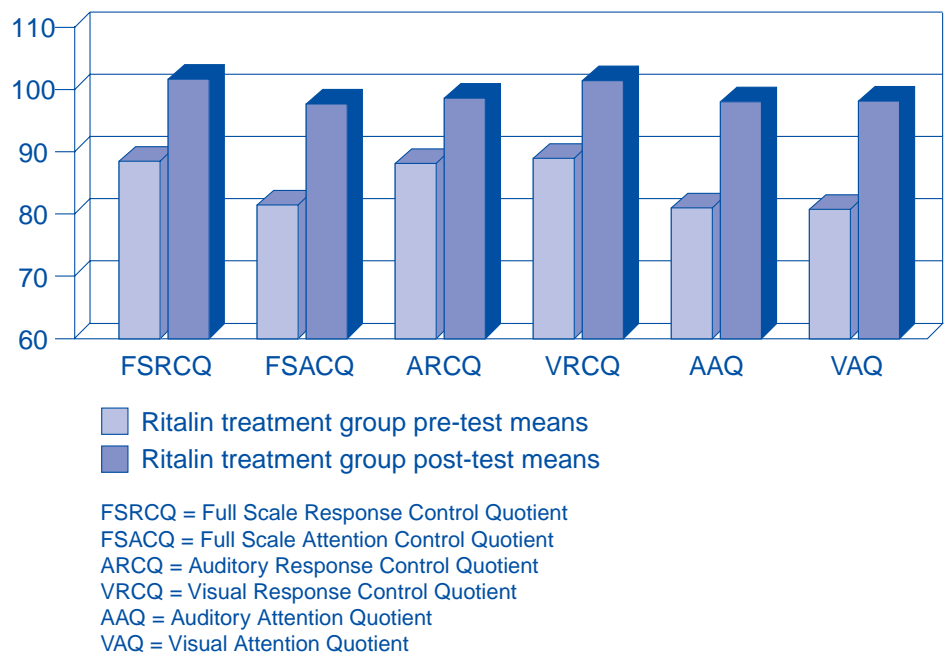

■ Alternative treatment group pre-test means
■ Alternative treatment group post-test means

FSRCQ = Full Scale Response Control Quotient
FSACQ = Full Scale Attention Control Quotient
ARCQ = Auditory Response Control Quotient
VRCQ = Visual Response Control Quotient
AAQ = Auditory Attention Quotient
VAQ = Visual Attention Quotient

Figure 4. IVA/CPT Pre- and Post-treatment Mean Scores for the Ritalin Group

■ Ritalin treatment group pre-test means
■ Ritalin treatment group post-test means

FSRCQ = Full Scale Response Control Quotient
FSACQ = Full Scale Attention Control Quotient
ARCQ = Auditory Response Control Quotient
VRCQ = Visual Response Control Quotient
AAQ = Auditory Attention Quotient
VAQ = Visual Attention Quotient

Reviews of the physiological and anatomical brain abnormalities in AD/HD suggest AD/HD arises idiopathically or that such brain abnormalities are caused by a genetic predisposition.[83] If such anatomical and physiological abnormalities were to arise spontaneously in genetically susceptible individuals, without known biochemical cause(s), it would follow that optimal treatment of AD/HD should be palliative, symptom management with medications. The 70 studies that support the eight risk factor categories as well as the positive outcomes in this study suggest AD/HD does not arise spontaneously, but in fact is caused by a combination of factors. This evidence suggests the physiological and anatomical brain abnormalities in AD/HD are not pre-programmed and inevitable, but are instead an expression of genetic vulnerabilities to the noted risk factors. Certain individuals may have genetically-imposed, heightened requirements for certain nutrients. If such individuals are not provided with optimum targeted nutrition, they may be significantly more vulnerable to the physiological and anatomical brain abnormalities associated with AD/HD symptoms.

Regardless of the various biological, psychological, or psychosocial factors that are ultimately found to cause AD/HD, this study found that synergistic combinations of dietary supplements directed at the more probable underlying etiologies of AD/HD, as determined by previous studies,[6-74] were equivalent to Ritalin treatment as measured by improvements of attention and self-control using IVA/CPT testing. The means for both treatment groups demonstrating the greatest subject impairment were found in the Full Scale Attention Control Quotient and the Visual Attention Quotient. This is consistent with the validity study for the IVA/CPT, where "comparisons of pre- and post-IVA/CPT scores can reliably be interpreted to reflect possible medication, treatment, or environmental effects."[80]

These findings support the effectiveness of a combined vitamin, mineral, amino acid, probiotic, essential fatty acid, and phospholipid treatment in improving attention and self-control in children with AD/HD. This combined nutritional approach more or less addressed eight likely risk factors. Further studies that target nutritional treatments to the unique, a priori, laboratory-determined risk factors of each test subject would go far beyond such vague empiricism and potentially achieve even better outcomes, based on treatment of the unique biochemical heterogeneity of each individual test subject.

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