



Q96 Empirical Reports and Abstracts

Q96 is specifically formulated to provide essential nutritional support to the brain and central nervous system.

Q96 delivers a well-balanced blend of 36 vitamins, minerals, and amino acids to the brain in a safe and effective dose to boost mood stability, mental clarity, and overall brain health in both children and adults. A proprietary 96-hour micronization and nano-chelation process increases the bioavailability of these nutrients for maximum nutrient uptake in the brain.

Q96 has been studied in a variety of human conditions and is backed by scientific research at fourteen universities in four countries, as well as research published in peer-reviewed journals.

Twenty published studies demonstrating effectiveness have led to several ongoing double-blind placebo controlled clinical trials. All research has been conducted independently with no funding from Q Sciences.

Empirical Reports

1. Efficacy And Cost Of Micronutrient Treatment Of Childhood Psychosis. *BMJ Case Report*, Rodway, M., Vance, A., Watters, A., Lee, H., Elske, B., & Kaplan, B.J. (2012).
2. Feasibility Of A Nutritional Supplement As Treatment For Pediatric Bipolar Spectrum Disorders. *Journal of Alternative and Complementary Medicine*, 18(7), 678-685. Frazier, E., Fristad, M., & Arnold, E. (2012).
3. Effects Of Micronutrients On Stress And Trauma After An Earthquake: RCT evidence comparing formulas and doses. *Human Psychopharmacology: Clinical and Experimental*. Rucklidge, J., Andridge, R., Gorman, B., Blampied, N., Gordon, H., & Boggis, A. (2012).
4. Post-Earthquake Psychological Functioning in Adults with Attention-Deficit/Hyperactivity Disorder: Positive Effects of Micronutrients on Resilience. *New Zealand Journal of Psychology*, 40(4). Rucklidge, J., & Blampied, N. (2011).
5. Micronutrients Reduce Stress And Anxiety In Adults With Attention-Deficit Hyperactivity Disorder Following A 7.1 Earthquake. *Psychiatry Res.* 189(2). Rucklidge, J., Johnston, J., Harrison, R., & Boggis, A. (2011).
6. Can Micronutrients Improve Neurocognitive Functioning In Adults With ADHD And Severe Mood Dysregulation? A pilot study. *Journal of Alternative and Complementary Medicine*. 17(2). Rucklidge, J., Johnstone, J., & Harrison, R. (2011).
7. Safety And Tolerability Of A Complex Micronutrient Formula Used In Mental Health: A compilation of eight datasets. *BMC Psychiatry*, 11(62). Simpson, J.S.A., Crawford, S.G., Goldstein, E.T., Field, C., Burgess, E., & Kaplan, B.J. (2011).
8. Effect Of Micronutrients On Behavior And Mood In Adults With ADHD: Evidence from an 8-week open label trial with natural extension. *Journal of Attention Disorders*, 15(1), 79-91. Rucklidge, J., Taylor, M., & Whitehead, K. (2011).
9. Database Analysis Of Children And Adolescents With Bipolar Disorder Consuming A Micronutrient Formula. *BMC Psychiatry*, 10(74). Rucklidge, J., Gately, D., & Kaplan, B.J. (2010).
10. Successful Treatment Of Bipolar Disorder II And ADHD With A Micronutrient Formula: A Case Study. *CNS Spectrums*. 15(5), 231-237. Rucklidge, J., & Harrison, R. (2010).

11. Micronutrients Versus Standard Medication Management In Autism: a naturalistic case-control study. *Journal of Child and Adolescent Psychopharmacology*, 20(2), 95-103. Mehl-Madrona, L., Leung, B., Kennedy, C., Paul, S., & Kaplan, B.J. (2010).
12. Database Analysis of Adults with Bipolar Disorder Consuming a Micronutrient Formula. *Clinical Medical Insights: Psychiatry*, 2, 3-16. Gately, D., & Kaplan, B.J. (2009).
13. Successful Treatment Of OCD With A Micronutrient Formula Following Partial Response To Cognitive Behavioral Therapy (CBT): a case study. *Journal of Anxiety Disorders*, 23, 836–840. Rucklidge, J. J. (2009).
14. Multinutrient Supplement As Treatment: Literature Review And Case Report Of A 12-Year-Old Boy With Bipolar Disorder. *Journal of Child and Adolescent Psychopharmacology*, 19(4), 453-460. Frazier, E., Fristad, M., & Arnold, L. (2009).
15. Improved Mood And Behavior During Treatment With A Mineral-Vitamin Supplement: an open-label case series of children. *Journal of Child and Adolescent Psychopharmacology*, 14(1), 115-122. Kaplan, B.J., Fisher, J.E., Crawford, S.G., Field, C.J., & Kolb, B. (2004).
16. Diet Can Stimulate Functional Recovery And Cerebral Plasticity After Prenatal Cortical Injury In Rats. *Soc Neuro Abs*, 29. Halliwell, C., & Kolb, B. (2003).
17. Treatment Of Mood Liability And Explosive Rage With Minerals And Vitamins: two case studies in children. *Journal of Child and Adolescent Psychopharmacology*, 12(3), 203-218. Kaplan, B.J., Crawford, S.G., Gardner, B., & Farrelly, G. (2002).
18. Nutritional Approach To Bipolar Disorder. *Journal of Clinical Psychiatry*, 64(3), 338-339. Simmons, M. (2003).
19. Do Vitamins Or Minerals (Apart From Lithium) Have Mood---Stabilizing Effects? [Commentary]. *Journal of Clinical Psychiatry*, 62, 933---935. Popper, C. W. (2001).
20. Effective Mood Stabilization In Bipolar Disorder With A Chelated Mineral Supplement. *Journal of Clinical Psychiatry*, 62, 936-944. Kaplan, B. J., Simpson, J. S. A., Ferre, R. C., Gorman, C., McMullen, D., & Crawford, S. G. (2001)

Abstracts of Q96 Published Empirical Reports

1. Rodway, M., Vance, A., Watters, A., Lee, H., Elske, B., & Kaplan, B.J. (2012). Efficacy and cost of micronutrient treatment of childhood psychosis. *BMJ Case Reports*.

Psychosis is difficult to treat effectively with conventional pharmaceuticals, many of which have adverse long-term health consequences. In contrast, there are promising reports from several research groups of micronutrient treatment (vitamins, minerals, amino acids and essential fatty acids) of mood, anxiety and psychosis symptoms using a complex formula that appears to be safe and tolerable. We review previous studies using this formula to treat mental symptoms, and present an 11-year-old boy with a 3-year history of mental illness whose parents chose to transition him from medication to micronutrients. Symptom severity was monitored in three clusters: anxiety, obsessive-compulsive disorder and psychosis. Complete remission of psychosis occurred, and severity of anxiety and obsession symptoms decreased significantly ($p < 0.001$); the improvements are sustained at 4-year follow-up. A cost comparison revealed that micronutrient treatment was <1% of his inpatient mental healthcare. Additional research on broad-spectrum micronutrient treatment is warranted.

2. Frazier, E., Fristad, M., Arnold, E. (2012). Feasibility of a nutritional supplement as treatment for pediatric bipolar spectrum disorders. Department of Psychiatry, The Ohio State University. *Journal of Alternative and Complementary Medicine*, vol 18 (7), pp. 678-685.

Objective: Current psychotropic medications for childhood bipolar spectrum disorders (BPSD) are associated with significant adverse events. As nutrients play an important role in physical and mental health, they may be useful in treating mood disorders with few side effects. This open label study explored the feasibility of testing therapeutic effects of a multi-nutrient supplement for pediatric BPSD.

Design: The supplement was started at one capsule t.i.d. and escalated to a goal of four capsules t.i.d., which eight children attained. Four (4) of these increased to the maximum dose, five capsules t.i.d. Mood symptoms were assessed seven times over 8 weeks.

Subjects: Ten (10) children, age 6–12 with BPSD, were enrolled in 6.5 months. Seven (7) participants completed the full trial. Three (3) dropped out due to palatability and/or adherence issues.

Results: Mean medication adherence was 91%. With one-tailed nonparametric Fisher's randomization tests, intent-to-treat analyses demonstrated a 37% decrease in depression scores ($p < 0.06$) and a 45% decrease in mania scores ($p < 0.01$) from the start of treatment through final visit, suggesting improvement and possible treatment response. Study completers demonstrated significant decreasing trends in both depression and mania scores from baseline to final visit ($p < 0.05$). Side-effects were minor and transient, mostly temporary gastric discomfort. Conclusions: Future randomized, placebo controlled trials of the supplement are warranted and feasible.

3. Rucklidge, J., Andridge, R., Gorman, B., Blampied, N., Gordon, H., & Boggis, A. (2012). Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses. *Human Psychopharmacology: Clinical and Experimental*.

Objective: To compare two micronutrient (vitamins and minerals) formulas (Berocca™ and CNE™) and assess their impact on emotions and stress related to the 6.3 earthquake on February 22nd 2011 in Christchurch, New Zealand.

Methods: 91 adults experiencing heightened anxiety or stress 2–3 months following the earthquake were randomized to Berocca™, CNE™ low dose (CNE4), or CNE™ high dose (CNE8), for 28 days and monitored weekly via on-line questionnaires and followed 1 month post-trial. A nonrandomized control group ($n = 25$) completed questionnaires at baseline and 4 weeks.

Results: All treatment groups experienced significant declines in psychological symptoms ($p < .001$). CNE™ groups experienced greater reduction in intrusive thoughts as compared with Berocca™ ($p = .05$), with no group differences on other measures of psychological symptoms. However, CNE8 group reported greater improvement in mood, anxiety, and energy ($p < .05$) with twice as many reporting being “much” to “very much” improved and five times more likely to continue taking CNE™ post-trial than Berocca™ group.

Treated participants had better outcomes on most measures over 4 weeks as compared to controls.
Conclusions: This study supports micronutrients as an inexpensive and practical treatment for acute stress following a natural disaster with a slight advantage to higher doses.

4. Rucklidge, J., & Blampied, N. (2011). Post-Earthquake Psychological Functioning in Adults with Attention-Deficit/Hyperactivity Disorder: Positive Effects of Micronutrients on Resilience. *New Zealand Journal of Psychology*, 40(4).

The September, 2010, 7.1 magnitude earthquake in Christchurch, New Zealand, provided an opportunity to study the after effects of a major earthquake where death and injury were absent. It created a natural experiment into the protective effects on well being of taking the micronutrient supplement, in a group of 33 adults diagnosed with ADHD who had been assessed prior to the earthquake. Fortuitously, 16 were currently taking the supplement as part of on going research at the time of the quake, while 17 were not (they had completed their trial or were waiting to begin consumption). The Depression Anxiety and Stress Scale (DASSy 42) which had been administered at varying times before the earthquake on recruitment into the micronutrient study was administered by telephone 7y 10 and again 14y 18 days post earthquake to volunteer, earthquake exposed participants. A modified Brinley plot analysis of the individual DASSy 42 scores showed that the 16 participants on the nutritional supplement were more resilient to the effects of the earthquake than the 17 individuals not taking the supplement. This effect was particularly marked for depression scores.

5. Rucklidge, J., Johnston, J., Harrison, R., & Boggis, A. (2011). Micronutrients reduce stress and anxiety in adults with attention-deficit/hyperactivity disorder following a 7.1 earthquake. *Psychiatry Res.* 189(2).

The role of good nutrition for resilience in the face of stress is a topic of interest, but difficult to study. A 7.1 earthquake took place in the midst of research on a micronutrient treatment for Attention-Deficit/Hyperactivity Disorder (ADHD), providing a unique opportunity to examine whether individuals with ADHD taking micronutrients demonstrated more emotional resilience post-earthquake than individuals with ADHD not taking micronutrients. Thirty-three adults with ADHD were assessed twice following the earthquake using a measure of depression, anxiety and stress also completed at some point pre-earthquake (baseline). Seventeen were not taking micronutrients at the time of the earthquake (control group), 16 were (micronutrient group). While there were no between-group differences one week post-quake (Time 1), at two weeks post-quake (Time 2), the micronutrient group reported significantly less anxiety and stress than the controls (effect size 0.69). These between group differences could not be explained by other variables, such as pre- earthquake measures of emotions, demographics, psychiatric status, and personal loss or damage following the earthquake. The results suggest that micronutrients may increase resilience to ongoing stress and anxiety associated with a highly stressful event in individuals with ADHD and are consistent with controlled studies showing benefit of micronutrients for mental health.

6. Rucklidge, J., Johnstone, J., & Harrison, R. (2011). Can micronutrients improve neurocognitive functioning in adults with ADHD and severe mood dysregulation? A pilot study. *Journal of Alternative and Complementary Medicine.* 17(2).

Objective: Little research has investigated how micronutrients (minerals and vitamins) affect cognitive functioning despite preliminary studies showing they may improve psychiatric functioning.

Intervention: This pilot study investigated the impact of a 36-ingredient micronutrient formula consisting mainly of vitamins and minerals on neurocognitive functioning in 14 adults with Attention-Deficit/Hyperactivity Disorder (ADHD) and severe mood dysregulation (SMD). Design: The formula was consumed in an open-label trial over an 8 week period.

Outcome Measures: The participants completed tests of memory (Wide Range Assessment of Memory and Learning) and executive functioning (Delis-Kaplan Executive Functioning System and Conners Continuous Performance Test) at baseline and at the end of the trial. A gender and age matched control group of 14 non-ADHD adults not taking the formula were assessed on the same tests 8 weeks apart in order to investigate the impact of practice on the results.

Results: There were no group differences in ethnicity, socio-economic status and estimated IQ. Significant improvement was observed in the ADHD group, but not the control group, across a range of verbal abilities

including verbal learning, verbal cognitive flexibility and fluency, and verbal inhibition. These neurocognitive improvements were large and consistent with improved psychiatric functioning. No changes were noted above a practice effect in visual-spatial memory and there were no improvements noted in reaction time, working memory or rapid naming for either groups.

Conclusions: Although the pilot and open label design of the study limits the generalizability of the results, it supports a growing body of literature recognizing the importance of nutrients for mental health and cognition. The results also provide evidence supporting the need for randomized clinical trials of micronutrients as well as other experimental studies in order to better assess whether improved neurocognitive functioning may contribute to improved psychiatric symptoms.

7. Simpson, J.S.A., Crawford, S.G., Goldstein, E.T., Field, C., Burgess, E., & Kaplan, B.J. (2011). Safety and tolerability of a complex micronutrient formula used in mental health: A compilation of eight datasets. BMC Psychiatry, 11(62).

Background: Theoretically, consumption of complex, multi-nutrient formulations of vitamins and minerals should be safe, as most preparations contain primarily the nutrients that have been in the human diet for millennia, and at safe levels as defined by the Dietary Reference Intakes. However, the safety profile of commercial formulae may differ from foods because of the amounts and combinations of nutrients they contain. As these complex formulae are being studied and used clinically with increasing frequency, there is a need for direct evaluation of safety and tolerability.

Objectives: The aim of this project was to compile all known safety and tolerability data collected on one complex nutrient formula.

Data sources and results: Data were assembled from all the known published and unpublished studies for the complex formula with the largest amount of published research in mental health. Biological safety data from 144 children and adults were available from six sources: there were no occurrences of clinically meaningful negative outcomes/effects or abnormal blood tests that could be attributed to toxicity. Adverse event (AE) information from 157 children and adults was available from six studies employing the current version of this formula, and only minor, transitory reports of headache and nausea emerged. Only one of the studies permitted a direct comparison between micronutrient treatment and medication: none of the 88 pediatric and adult participants had any clinically meaningful abnormal laboratory values, but tolerability data in the group treated with micronutrients revealed significantly fewer AEs and less weight gain.

Conclusions: This compilation of safety and tolerability data is reassuring with respect to the broad-spectrum approach that employs complex nutrient formulae as a primary treatment.

8. Rucklidge, J., & Harrison, R. (2010). Successful Treatment of Bipolar Disorder II and ADHD with a Micronutrient Formula: A Case Study. CNS Spectrums. 15(5), 231-237.

Bipolar Disorder with co-occurring Attention-Deficit/Hyperactivity Disorder (ADHD) is a challenge to treat. Ten previous reports have shown potential benefit of a micronutrient treatment (consisting mainly of vitamins and minerals) for various psychiatric symptoms, including mood and ADHD. This case study aimed to investigate the longer impact of the micronutrients on both psychiatric and neurocognitive functioning in an ABAB design with one year follow up. A 21-year old female with Bipolar II Disorder, ADHD, Social Anxiety and Panic Disorder entered an open-label trial using a nutritional treatment following a documented 8-year history of ongoing psychiatric symptoms not well managed by medications. After 8 weeks on the formula she showed significant improvements in mood, anxiety and hyperactivity/impulsivity. Blood test results remained normal after 8 weeks on the formula. She did not report any adverse side effects associated with the treatment. She then chose to come off the formula; after 8 weeks her depression scores returned to baseline, and anxiety and ADHD symptoms worsened. The formula was reintroduced, showing gradual improvement in all psychiatric symptoms. KT's case represents a naturalistic ABAB design showing on-off control of symptoms. After one year, she is now in remission of all mental illness. Neurocognitive changes mirrored behavioral changes, showing improved processing speed, variability in response and verbal memory. A placebo response and expectancy effects cannot be ruled out although previous poor response to treatment and the duration of the current positive response decrease the likelihood these other factors better explain change. These consistently positive outcomes alongside an absence of side effects indicate that further research, particularly larger and more controlled trials, is warranted using this multi-nutrient approach.

9. Rucklidge, J., Gately, D., & Kaplan, B.J. (2010). Database analysis of children and adolescents with Bipolar Disorder consuming a micronutrient formula. BMC Psychiatry, 10(74).

Background: Eleven previous reports have shown potential benefit of micronutrient treatment for psychiatric symptoms. The current study asked whether children (7-18 years) with pediatric bipolar disorder (PBD) benefited from the same micronutrient formula; the impact of Attention-Deficit/Hyperactivity Disorder (ADHD) on their response was also evaluated.

Methods: Data were available from 120 children whose parents reported a diagnosis of PBD; 79% were taking psychiatric medications that are used to treat mood disorders; 24% were also reported as ADHD. Using Last Observation Carried Forward (LOCF), data were analyzed from 3 to 6 months of micronutrient use.

Results: At LOCF, mean symptom severity of bipolar symptoms was 46% lower than baseline (effect size (ES) >0.78) ($p < 0.001$). In terms of responder status, 46% experienced >50% improvement at LOCF, with 38% still taking psychiatric medication (52% drop from baseline) but at much lower levels (74% reduction in number of medications being used from baseline). The results were similar for those with both ADHD and PBD: a 43% decline in PBD symptoms (ES = 0.72) and 40% in ADHD symptoms (ES = 0.62). An alternative sample of children with just ADHD symptoms ($n = 41$) showed a 47% reduction in symptoms from baseline to LOCF (ES = 1.04). The duration of reductions in symptom severity suggests that benefits were not attributable to placebo/expectancy effects. Similar findings were found for younger and older children and for both sexes.

Conclusions: The data are limited by the open label design, the lack of a control group, and the inherent self-selection bias. While these data cannot establish efficacy, the results are consistent with a growing body of research suggesting that micronutrients appear to have therapeutic benefit for children with PBD with or without ADHD in the absence of significant side effects and may allow for a reduction in psychiatric medications while improving symptoms. The consistent reporting of positive changes across multiple sites and countries are substantial enough to warrant a call for randomized clinical trials using micronutrients.

10. Mehl-Madrona, L., Leung, B., Kennedy, C., Paul, S., & Kaplan, B.J. (2010). Micronutrients versus standard medication management in autism: a naturalistic case-control study. Journal of Child and Adolescent Psychopharmacology, 20(2), 95-103.

Autism spectrum disorder (ASD) is often accompanied by self-injurious behavior (SIB), aggression, and tantrums, symptoms that have reportedly improved with micronutrient (vitamins and minerals) treatment. The current study took advantage of naturally-occurring differences in parental preferences for treatment approaches. The Micronutrient Group asked for treatment without pharmaceuticals ($n = 44$, aged 2-28 yrs at entry ($M = 8.39, + 5.58$)). Their records were matched with those of 44 similar children whose families requested conventional treatment (Medication Group). Both groups improved on both the Childhood Autism Rating Scale and the Childhood Psychiatric Rating Scale (all p 's < 0.0001). Both groups also exhibited significant decreases in total Aberrant Behavior Checklist scores, but the Micronutrient Group's improvement was significantly greater, $p < 0.0001$. SIB Intensity was lower in the Micronutrient Group at the end of the study ($p = 0.005$), and improvement on Clinical Global Impressions was greater for the Micronutrient Group, $p = 0.0029$. It is difficult to determine whether the observed changes were exerted through improvement in mood disorder or through an independent effect on autistic disorder. There were some advantages to treatment with micronutrients: lower activity level, less social withdrawal, less anger, better spontaneity with the examiner, less irritability, lower intensity SIB, markedly fewer adverse events, and less weight gain. Advantages of medication management were insurance coverage, fewer pills, and less frequent dosing.

11. Rucklidge, J.J., Taylor, M. R., Whitehead, K. A. (2010). Impact of a micronutrient formula on ADHD and mood Dysregulation in adults with ADHD: Evidence from an 8-week open label trial with natural follow-up. Journal of Attention Disorders.

Objective: To investigate the impact of a 36-ingredient micronutrient formula consisting mainly of minerals and vitamins in the treatment of adults with both Attention-deficit/hyperactivity Disorder (ADHD) and severe mood Dysregulation (SMD).

Method: 14 medication-free adults (9 men, 5 women; 18-55 years) with ADHD and SMD completed an

8-week open-label trial.

Results: A minority reported transitory mild side effects. Significant improvements were noted across informants (self, observer, clinician) on measures of inattention and hyperactivity/impulsivity, mood, quality of life, anxiety, and stress all with medium to very large effect sizes (all p 's < .01); however, the mean of inattention remained in a clinical range whereas the means on measures of mood and hyperactivity/impulsivity were normalized. Follow-up data showed maintenance of changes or further improvement for those who stayed on the micronutrients.

Conclusions: Although this study, as an open trial, does not in itself prove efficacy, it provides preliminary evidence supporting the need for a randomized clinical trial of micronutrients as treatment for the more complex presentations of ADHD.

12. Gately, D., Kaplan, B.J. (2009). Database analysis of adults with bipolar disorder consuming a micronutrient formula. *Clinical Medicine: Psychiatry*, 4, 3-16.

Background: Bipolar disorder is a lifelong problem with imperfect available treatments. Recent research has shown potential benefit of nutritional treatment for mood symptoms. The goal of the current study was to determine whether adults with bipolar disorder reported treatment benefit from consuming a micronutrient formula.

Methods: Self-report data were available from 682 adults who reported a diagnosis of bipolar disorder; 81% were taking psychiatric medications. Those reporting additional diagnoses were excluded, as well as those who provided data <60 times during 180 days of using the micronutrients, leaving 358 for analysis.

Results: Mean symptom severity was 41% lower than baseline after 3 months (effect size = 0.78), and 45% lower after 6 months (effect size = 0.76) (both paired t-tests significant, $p < 0.001$). In terms of responder status, 53% experienced >50% improvement at 6 months. Half the sample were taking medications approved for bipolar disorder (lithium, anticonvulsants, atypical antipsychotics), and half were either medication-free or taking other medications: the magnitude of treatment benefit did not differ between these two groups. Regression analyses indicated that decreased symptom severity over the 6 months was associated with increasing micronutrient dosage and with reducing medication. Symptom improvements were significant and sustained at 6 months, suggesting that benefits were not attributable to placebo/expectancy effects.

Conclusions: Further research on this micronutrient formula is warranted.

13. Rucklidge, J. J. (2009). Successful treatment of OCD with a micronutrient formula following partial response to CBT: A case study. *Journal of Anxiety Disorders*, 23, 836–840.

Obsessive Compulsive Disorder (OCD) affects 0.5–2% of young people many of whom are resistant to conventional treatments. This case study describes an 18-year-old male with OCD who first underwent cognitive behavioral therapy (CBT) for a 1-year period with a modest response (his OCD had shifted from severe to moderate). Within a year, his anxiety had deteriorated back to the severe range and he now had major depression. He then entered an ABAB design trial using a nutritional formula consisting mainly of minerals and vitamins (together, known as micronutrients). After 8 weeks on the formula, his mood was stabilized, his anxiety reduced, and his obsessions were in remission. The treatment was then discontinued for 8 weeks, during which time his obsessions and anxiety worsened and his mood dropped. Reintroduction of the formula again improved the symptoms. This case illustrates the importance of considering the effect micronutrients have on mental illness.

14. Frazier, E., Fristad, M., & Arnold, L. (2009). Multinutrient supplement as treatment: literature review and case report of a 12-year-old boy with bipolar disorder. *Journal of Child and Adolescent Psychopharmacology*, 19(4), 453-460.

Early-onset bipolar disorder has significant morbidity and mortality. Development of safe, effective treatments to which patients will adhere is critical. Pharmacologic interventions for childhood bipolar spectrum disorders are limited and are associated with significant risk for adverse events (Kowatch et al 2005). Diet and nutrition research suggests vitamins, minerals, and other nutrients are important underpinnings of general physical and mental health; further, they may even be useful in treating mood

dysregulation by providing a more favorable risk--benefit ratio than contemporary psychotropic agents (Kaplan, Crawford, Field, & Simpson 2007).

This article reviews the literature on multi-nutrient supplementation and mental health, and examines a case study of a 12-year-old boy with bipolar disorder and comorbid diagnoses treated for 6 years with conventional medication and finally a multi-nutrient supplement.

The multi-nutrient supplement in this case study is a 36-ingredient supplement containing sixteen minerals, fourteen vitamins, three amino acids and three antioxidants. It was used to treat a 12- year old boy initially diagnosed with bipolar disorder not otherwise specified (BPY NOS) at age 6, whose diagnosis evolved by age 10 to bipolar I (BPY I), mixed, with psychotic features. He also met criteria for generalized anxiety disorder by age 8 and obsessively compulsive disorder by age 10. After six years of conventional treatment (ages 6y 12), he received fourteen months of the supplement. Symptom manifestation over seven years is described in conjunction with treatment history. The supplement resulted in superior outcome to conventional treatment.

15. Kaplan, B.J., Fisher, J.E., Crawford, S.G., Field, C.J., & Kolb, B. (2004). Improved mood and behavior during treatment with a mineral-vitamin supplement: an open-label case series of children. *Journal of Child and Adolescent Psychopharmacology*, 14(1), 115-122.

Several studies have demonstrated that psychiatric symptoms such as depression, mood swings, and aggression may be ameliorated by supplementation with broad--based nutrient formulas containing vitamins, minerals, and sometimes essential fatty acids. These findings have been reported in young criminal offenders as well as in adults with mood disturbance and other psychiatric disorders. The purpose of the current case series was to explore the potential efficacy of a nutrient supplement in children. Children with mood and behavioral problems (N = 11; 7 boys, 4 girls; 8–15 years old) participated; 9 completed this open-label trial. Parents completed the Child Behavior Checklist (CBCL), Youth Outcome Questionnaire (YOQ), and Young Mania Rating Scale (YMRS) at entry and following at least 8 weeks of treatment. Intent--to--treat analyses revealed decreases on the YOQ ($p < 0.001$) and the YMRS ($p < 0.01$) from baseline to final visit. For the 9 completers, improvement was significant on seven of the eight CBCL scales, the YOQ, and the YMRS (p values from 0.05–0.001). Effect sizes for all outcome measures were relatively large. The findings suggest that formal clinical trials of broad nutritional supplementation are warranted in children with these psychiatric symptoms.

16. Halliwell, C., & Kolb, B. (2003). Diet can stimulate functional recovery and cerebral plasticity after prenatal cortical injury in rats. *Soc Neuro Abs*, 29.

Early cortical injury has been attributed to the consequential effects of various factors, such as alcohol, drug addiction, smoking, and inadequate nutrient intakes during periods of pregnancy and lactation, or delivery of infants by forceps, and premature deliveries. These are only a few examples of circumstances, or "injury", that may result in disorders ranging from mild learning difficulties to aggressive behavior. Injury to the cortex during the early years of development has been known to result in poor behavioral outcome into adulthood. Presently, the most common form of treatment includes a pharmacological agent, which may be accompanied with behavioral modification therapies supported by families. As an alternative form of therapy towards the treatment of early cortical injury, choline and a vitamin and mineral supplement were used to determine the possibilities of nutrition intervention in an animal model. The injuries were incurred by aspiration lesion at days three and four, and lesions were localized to the midline medial frontal cortex in some rats, while a different group of rats received lesions in the posterior parietal cortex. The pre and postnatal choline treated animals showed favorable results for the medial frontal lesions, and the postnatal vitamin supplement treated animals showed favorable results for treatment in both medial frontal and posterior parietal lesions. All animals were tested in adulthood indicating that nutrition intervention is very beneficial for alleviating some of the functional deficits commonly seen from early cortical injury.

17. Kaplan, B.J., Crawford, S.G., Gardner, B., & Farrelly, G. (2002). Treatment of mood liability and explosive rage with minerals and vitamins: two case studies in children. *Journal of Child and Adolescent Psychopharmacology*, 12(3), 203-218.

A micronutrient supplement containing a broad range of dietary minerals and vitamins is being examined for the treatment of mood liability in both adults and children (Kaplan et al. 2001; Popper 2001). During pilot work, two medication-free boys with mood liability and explosive rage were studied in an open--label

treatment followed by reversal and retreatment. One child was an 8-year-old with atypical obsessive-compulsive disorder, and the other was a 12-year-old with pervasive developmental delay. Both boys were monitored using the mood and temper items from the Conners Parent Rating Scale, as well as the Child Behavior Checklist. In addition, the boy with atypical obsessive-compulsive disorder was monitored with the child version of the Yale-Brown Obsessive Compulsive Scale. Both boys benefited from the micronutrient supplement when examined in ABAB designs: mood, angry outbursts, and obsession symptoms improved when initially treated, returned when not taking the supplement, and remitted when the micronutrient supplement was reintroduced. Both boys have been followed and are stable on the nutritional supplement for over 2 years. These cases suggest that mood lability and explosive rage can, in some cases, be managed with a mixture of biologically active minerals and vitamins, without using lithium or other traditional psychopharmacologic agents.

18. Simmons, M. (2003). Nutritional Approach to Bipolar Disorder. *Journal of Clinical Psychiatry*, 64, 338.

Summary: In a letter to the editor of the *Journal of Clinical Psychiatry* Dr. Miles Simmons, a psychiatrist in private practice in Brunswick, Maine reported on his clinical experience with the Q96® formula. Impressed by a striking response in a patient who approached him, and after discussing the issues with several of his treatment-resistant patients, he conducted an open trial study with 19 patients from his private practice under careful supervision. His results corroborate Dr. Kaplan's initial findings. All patients met the DSM-IV criteria for bipolar I (n = 14) or bipolar II (n = 5) and were followed for a mean of 13 months. Of the 19 patients, 16 were already taking medications (mean = 2.7 psychiatric medications). Dr. Simmons observed that "12 of the 19 patients showed marked clinical improvement, 3 showed moderate improvement, and 1 showed mild improvement" (84%). Thirteen of the 16 medicated patients were able to completely discontinue psychiatric medications over an average of 5.2 weeks (range, 3 to 10 weeks) and maintained stability on the Q96® formula alone.

19. Popper, C.W. (2001). Do vitamins or minerals (apart from lithium) have mood-stabilizing effects? *Journal of Clinical Psychiatry*, 62, 933-935.

Summary: Harvard University (McLean Hospital) clinician, psycho-pharmacologist and Psychiatrist Dr. Charles Popper published commentary including the results of his clinical experience with the Q96® formula. In Dr. Popper's practice, out of 22 patients (10 adult, 9 adolescent, 3 preadolescent) that clinically met criteria for bipolar disorder, 19 showed what he judged to be a positive response. Of the 15 patients who were being treated with medications when they began the nutritional supplement, 11 patients have been stable for 6 to 9 months without psychiatric medications. Dr. Popper's findings support Dr. Kaplan's observations that over 80% of patients saw significant improvement.

20. Kaplan, B. J., Simpson, J. S. A., Ferre, R. C., Gorman, C., McMullen, D., & Crawford, S. G. (2001). Effective mood stabilization in bipolar disorder with a chelated mineral supplement. *Journal of Clinical Psychiatry*, 62, 936-944.

Background: To determine in open trials the therapeutic benefit of a nutritional supplement for bipolar disorder.

Method: The sample consisted of 11 patients with DSM-IV-diagnosed bipolar disorder aged 19 to 46 years, who were taking a mean of 2.7 psychotropic medications each at a study entry. Three additional patients dropped out prematurely. The intervention is a broad-based nutritional supplement of dietary nutrients, primarily chelated trace minerals and vitamins, administered in high doses. At study entry and periodically thereafter, patients were assessed with the Hamilton Rating Scale for Depression (HAM-D), the Brief Psychiatric Rating Scale (BPRS), and the Young Mania Rating Scale (YMRS).

Results: For those who completed the minimum 6-month open trial, symptom reduction ranged from 55% to 66% on the outcome measures; need for psychotropic medications decreased by more than 50%. Paired t tests revealed treatment benefit on all measures for patients completing the trial: HAM-D mean score at entry = 19.0, mean score at last visit = 5.4, t = 5.59, df = 9, p < .01; BPRS mean score at entry = 35.3, mean score at last visit = 7.4, t = 2.57, df = 9, p < .05; YMRS mean score at entry = 15.1, mean score at last visit = 6.0, t = 4.11, df = 9, p < .01. The effect size for the intervention was large (> .80) for each measure. The number of psychotropic medications decreased significantly to a mean ± SD of 1.0 ± 1.1 (t = 3.54, df = 10, p < .01). In some cases, the supplement replaced psychotropic medications and the patients

remained well. The only reported side effect (i.e. nausea) was infrequent, minor, and transitory.

Conclusion: Some cases of bipolar illness may be ameliorated by nutritional supplementation. A randomized, placebo controlled trial in adults with bipolar I disorder is currently underway, as well as open trials in children.

Additional Articles on Micronutrients in Mental Health

1. Hurt E., Lofthouse N., & Arnold L.E. (2011). Complementary and Alternative Biomedical Treatments for ADHD. *Psychiatric Annals*, 41(1).
2. Kaplan, B.J. & Leung, B. (2011). Micronutrient treatment of mental disorders. *Integrative Medicine*, 10(3).
3. Shaw I., Rucklidge J. J., Hughes R. N. (2010). A possible biological mechanism for the B Vitamins altering behavior in ADHD. *Pharmaceutical Medicine*, 24 (5), 1-6.
4. McCann, J.C., & Ames, B.N. (2009). Vitamin K, an example of triage theory: Is micronutrient inadequacy linked to diseases of aging? *The American Journal of Clinical Nutrition*, 90, 889-907.
5. Rucklidge, J.J., Johnstone, J., & Kaplan, B.J. (2009). Nutrient supplementation approaches in the treatment of ADHD. *Expert Review of Neurotherapeutics*, 9(4), 461-476.
6. Kaplan, B.J., Crawford, S., Field, C., & Simpson, J.S.A. (2007). Vitamins, minerals, and mood. *Psychological Bulletin*, 33(5), 747-760.
8. Kaplan, B.J. & Shannon, S. (2007). Nutritional aspects of child and adolescent psychopharmacology. *Psychiatric Annals*, 37(7), 519-528. Reprinted in *Pediatrics Annals*, 36(9), 600-609.
9. Ames, B.N. (2004). A role for supplements in optimizing health: The metabolic tune-up. *Archives of Biochemistry and Biophysics*, 423, 227-234.