Micronutrient Treatment for Adolescents with Severe Mood Dysregulation:
A Single-Case Reversal Design Analysis

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Abstract

Research has examined the effects of micronutrients on mood in both healthy and psychiatric populations. EMPowerplus (EMP+) is a formula containing a wide range of vitamins and minerals. It has been examined for the treatment of mood instability, anxiety, Attention Deficit Hyperactivity Disorder (ADHD) and autism. The present study trialled EMP+ with five adolescents, aged 16-21, all with Severe Mood Dysregulation (SMD) as well as co-occurring psychiatric diagnoses i.e. ADHD, anxiety and substance abuse. The sample reflects a group of adolescents with complex psychiatric presentations and therefore difficult to treat. An ABAB (off-on-off-on) research design was employed. An open-label trial (8 weeks) of the micronutrients was followed by a withdrawal phase (8 weeks) and then a reinstatement of the micronutrients for a longer period of time (up to 24 weeks). There were in-depth pre and post assessments and on-going monitoring of the participants for the duration of the study. Clinically significant improvements in symptoms and functioning were demonstrated in three/four participants. Two participants demonstrated on-off control of psychiatric symptoms, with a reversal and replication of treatment effect. Further, one participant demonstrated clinically significant improvements in mood and functioning while on the micronutrients; however, he was lost to follow up following the 7.1 earthquake, and a reversal was not obtained. One participant demonstrated a trend toward improvements in mood while on the micronutrients and subsequent deterioration during the wash-out phase. However, she decided to withdraw from the study at four weeks off to go on psychiatric medication. Further, one participant demonstrated a variable response. This study provides some further evidence that micronutrients may be an effective treatment for psychiatric symptoms, consistent with other reports. Further research, such as randomised clinical trials and studies investigating the mechanisms of action, appears warranted.
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1. Introduction

1.1 Background to Severe Mood Dysregulation

There has recently been a dramatic increase in the diagnosis of Bipolar Disorder (BD) in children and adolescents (Blader & Carlson, 2007; Pavuluri, Birmaher, & Naylor, 2005). This increase in diagnosis has generated controversy surrounding the disorder. Specifically, children with symptoms of Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) and a chronically irritable mood who do not present with classic acute episodes of mania and depression have frequently been diagnosed with BD. A National Institute of Mental Health (NIMH) working group, led by Ellen Leibenluft, addressed this controversy by constructing the diagnostic label of “severe mood dysregulation” (SMD). This label refers to children with chronic irritability, hyperarousal (i.e. insomnia, restlessness, distractibility, racing thoughts) and emotional reactivity. These children display frequent emotional outbursts and persistent negative mood. Further, these children lack other symptoms specific to mania. Given that it is unclear whether these children truly belong in the Bipolar Spectrum, the term SMD appears to characterise them better (Leibenluft, Charney, Towbin, Bhangoo, & Pine, 2003). The SMD term is an alternative to labeling these individuals as “broad phenotype bipolar disorder”. SMD appears to be non-specific to any Diagnostic and Statistical Manual of Mental Disorders – IV - TR (DSM-IV-TR; American Psychological Association) diagnostic category.

According to the DSM-IV, BD is characterised by episodes of mania, hypomania, or mixed state, and depression. Distinct episodes with a significant change from baseline functioning are required for the diagnosis of BD. BD-I is assigned if the manic episode lasts for at least seven days and BD-II is assigned if the manic episode lasts at least four days (hypomania). When episodes are shorter than four days, Bipolar Disorder Not Otherwise
Specified (BD-NOS) is sometimes assigned. The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines suggest that BD NOS should be assigned to youth with “manic symptoms lasting hours to less than 4 days or for those with chronic manic-like symptoms representing their baseline level of functioning” (Action, 2007, p 115). The Course of Bipolar Youth study found that 96 percent of those classified as BD-NOS did not meet full DSM-IV criteria because their episodes were too short (Birmaher et al., 2006). These youth with BD-NOS youth showed similar clinical features and family history to those with BD-I, and up to a third of them switched to either BD-I or II within a few years (Birmaher, et al., 2006). In contrast, those with non-episodic irritability (SMD) appear to be at risk for depression. The Great Smoky Mountains Study found that youth meeting criteria for SMD at age 10 had an elevated risk for Major Depressive Disorder (MDD) at age 18 (Birmaher, et al., 2006). Leibenluft and colleagues (2006) found that episodic irritability at time 1 (mean age 13) predicted ADHD at time 2 (mean age 16) and MDD at time 3 (mean age 22). The association with MDD is consistent with other findings (Burke, Loeber, Lahey, & Rathouz, 2005). In summary, the longitudinal course of youth with SMD highlights that they should not be diagnosed as BD. Therefore, two distinct groups (episodic versus non-episodic) appear to be lumped into the BD-NOS category (Baroni, Lunsford, Luckenbaugh, Towbin, & Leibenluft, 2009).

1.2 Treatments for SMD

In terms of psychopharmacological treatments for SMD, the choice is between medications specifically for ADHD or for mood lability. Stimulants such as methylphenidate are effective at reducing aggression (Connor, Glatt, Lopez, Jackson, & Melloni Jr, 2002); however, concerns that stimulants may induce mania in children with or at risk of BD have led to warnings against using them in children with ADHD and “manic-like” symptoms (see Waxmonsky &
Pariseau, 2009). Waxmonsky and colleagues (2008) conducted a study with children, aged 5 to 12 with ADHD. A subgroup of 33 children with ADHD and SMD was compared with a group of 68 children with ADHD without SMD (half also met criteria for ODD). Using a crossover design, the children were treated with methylphenidate and behavior modification therapy. In the SMD group, treatment was associated with a 34 percent reduction in scores on the Young Mania Rating Scale (YMRS) and a 31 percent reduction in scores on the Child Depression Rating Scale – R (CDRS-R). However, the SMD group still displayed elevated YMRS ratings, more ODD/CD symptoms, and greater impairment as rated by parents, at the end of the trial than those without SMD. The authors concluded that while conventional ADHD treatments are useful for children with ADHD and SMD, they do not eliminate all symptoms (Waxmonsky, et al., 2008).

Mood stabilising medications are another treatment option for children with SMD. However, mood stabilisers are associated with many side effects including adiposity, cardiac changes, neuromuscular effects, hypokinesias, and hyperandrogenism (Blader & Kafantaris, 2007; Ghaemi, Hsu, Rosenquist, Pardo, & Goodwin, 2006). A randomised double-blind placebo-controlled trial of lithium in youths aged 7 to 17 with SMD found no significant differences on clinical outcome measures between lithium and placebo (Dickstein et al., 2009). This was the first Randomised Clinical Trial (RCT) in youth with SMD, highlighting the critical need for treatment studies (Dickstein, et al., 2009). In summary, the limited studies examining treatments for SMD highlight that children and adolescents with SMD are a difficult group to successfully treat. Further research is needed on the treatment of SMD. In addition, alternative treatments should be explored.
1.3 Why micronutrients should be considered

Micronutrients, which are vitamins and minerals, are important in both physical and mental health. Micronutrients are involved in many brain functions, ranging from energy metabolism of nerve cells to the synthesis of neurotransmitters (Haller, 2005). In terms of energy metabolism of the brain, the brain accounts for 20 percent of the body’s supply of oxygen, although it only accounts for 2-2.7 percent of body weight. Glucose is the primary source of energy for the brain and metabolism of glucose is dependent on vitamins such as thiamin (Haller, 2005). The B-vitamins are important in maintaining an optimal blood supply to the brain and help to control blood levels of homocysteine (Haller, 2005). In terms of neurotransmitter synthesis, vitamins and minerals are essential cofactors in the synthesis of many neurotransmitters. More than one third of enzymes need a vitamin or mineral cofactor (Haller, 2005). Vitamins and minerals are also involved in neuronal receptor binding in that they can enhance or attenuate receptor binding of neurotransmitters (Haller, 2005). The integrity of axons and their myelin sheaths is dependent on vitamins, such as cobalamin and folate. Thiamin has an important role in nerve conduction (Haller, 2005). Micronutrients are important for normal brain function and therefore are a worthy consideration in the field of mental health. Micronutrient deficiencies may result in changes in brain function which then in turn result in behavioural changes (Haller, 2005). Early findings on the association between vitamin deficiencies and personality changes prompted further research examining the effects of vitamins on mood (Haller, 2005).

1.4 Association between micronutrient deficiencies and mood symptoms

Vitamin B9 (folate) can increase serotonin function and is a cofactor for enzymes that convert tryptophan into serotonin. It is involved in the synthesis of monoamine neurotransmitters
and involved in brain energy metabolism. Vitamin B12 (cobalamin) is also involved in the synthesis of monoamine neurotransmitters and is involved in the metabolism of folate. Therefore, a deficiency in vitamin B12 can subsequently result in a secondary deficiency in folate. Vitamin B1 (thiamine) is involved in the synthesis of acetylcholine, gamma-aminobutyric acid (GABA) and glutamate. Vitamin B6 (pyridoxine) is involved in the synthesis of many neurotransmitters and is important for normal brain development (Kaplan, Crawford, Field, & Simpson, 2007). It has been suggested that B-vitamin deficiencies may predispose a susceptible person to developing depression or may exacerbate a mood disorder that is already present (Abou-Saleh & Coppen, 1986). In terms of the relationship between B-vitamin deficiencies and mood, the majority of the research has been on folate (vitamin B9). Godfrey and colleagues (1990) found that in a sample of patients with major depression or schizophrenia, one third had borderline or deficient blood cell folate levels. In-patients with BD have been found to have low red blood cell folate, tested during an acute manic episode, compared with controls (Hasanah, Khan, Musalmah, & Razali, 1997). Bottiglieri and colleagues (2000) found that in a sample of depressed patients, half had low folate and cobalamine levels. Tolmunen and colleagues (2003) examined the relationship between dietary folate intake and depressive symptoms and found that individuals with low folate intake had a significantly higher risk of depressive symptomatology than individuals with high folate intake. Morris and colleagues (2000) found that serum and red blood cell folate levels were significantly lower in those with a lifetime diagnosis of major depression compared to those who had never been depressed. Vitamin E has important antioxidant properties and lower levels of serum vitamin E have been found in patients with major depression compared with normal controls (Maes et al., 2000).

Zinc is involved in the synthesis of protein and is a cofactor for a large number of enzymes. Zinc is important in neuronal and glial cells. Zinc may also play a role as an
antioxidant in the brain (Bray & Levy, 2005). Zinc is critical for normal brain development and is important for behavioural and cognitive functions (Bray & Levy, 2005). Lower serum levels of zinc have been found in treatment resistant depressed patients compared with normal controls (Maes et al., 1997). Calcium plays a role in the release of neurotransmitters and chemical signalling between and within cells. Calcium status is also dependent on the availability of Vitamin D (Kaplan, et al., 2007). Significantly lower plasma calcium has been found in both unipolar depressed patients and manic patients compared with healthy controls (Kaplan, et al., 2007). Iron is involved in the production of dopamine and metabolises tyrosine to dopamine. It is also involved in the synthesis of other neurotransmitters and myelin (Pinero & Connor, 2005). In addition, iron plays a role in producing Adenosine Triphosphate (ATP) energy in the brain. Iron is involved in many important “biochemical functions, including oxygen transport, electron transport, glucose metabolism, synthesis of neurotransmitters and myelin, and DNA replication in all organisms” (Pinero & Connor, 2005, p. 236) The brain has a high requirement for iron (Pinero & Connor, 2005). Maes and colleagues (1996) found that individuals with major depression had significantly lower serum iron and transferrin levels than normal controls.

1.5 Effect of individual micronutrient interventions on mood symptoms

As discussed above, micronutrient deficiencies are associated with psychiatric symptoms and therefore research has examined the effect of supplementation with individual micronutrients on mood (Kaplan & Shannon, 2007). Research has found beneficial effects of B-vitamin supplementation for patients with depressive and/or manic symptoms. In a RCT, thiamine (vitamin B1) supplementation, compared to placebo, was shown to improve mood in healthy women (not diagnosed with a mental disorder) and this effect was more pronounced in those who started the treatment with low thiamine levels (Benton, Griffiths, & Haller, 1997). Godfrey
and colleagues (1990), in a RCT with patients with depression (n = 24) or schizophrenia (n = 17) who were folate-deficient, found that supplementation with folic acid resulted in greater clinical improvement in the treatment group than in the placebo group at three and six months and that the differences became greater with time. Coppen and Bailey (2000), in an RCT of 127 adults with major depression taking fluoxetine, found that folic acid augmented the therapeutic effects of fluoxetine.

Research has also examined the effects of specific minerals on mental health (see review by Kaplan et al., 2007). In a case series of eight patients, chromium supplementation was found to be effective in the treatment of refractory mood disorders (McLeod & Golden, 2000). In a case series of five adults with dysthymic disorder, chromium was associated with symptom remission (McLeod, Gaynes, & Golden, 1999). In a RCT, chromium supplementation resulted in greater symptom remission than placebo in adults with atypical depression (Davidson, Abraham, Connor, & McLeod, 2003). Thys-Jacobs and colleagues (1998), in a RCT with 466 women aged 18 to 45 with premenstrual syndrome (PMS), found a 48 percent reduction in PMS symptoms, including negative affect, in those receiving calcium compared to a 30 percent reduction in those receiving placebo. By the third treatment cycle, all four symptom factors (negative affect, water retention, food cravings, and pain) were significantly reduced. The PMS Diary was used to assess treatment change (Thys-Jacobs, et al., 1998). Calcium is important for the release of neurotransmitters and an important cofactor for enzymes (Kaplan et al., 2007).

Magnesium is involved in the metabolism of carbohydrates and fats and converts them to ATP. It is also involved in synthesising nucleic acids, both DNA and RNA, as well as proteins. Furthermore, magnesium plays a role in transporting ions, such as potassium and calcium, across cell membranes. It is essential for a large number of biochemical reactions in the body such as maintaining normal nerve function (see Kaplan et al., 2007). Magnesium has been examined as
an adjunctive treatment for bipolar disorder. Heiden and colleagues (1999), in a case series of 10 adults with severe treatment-resistant mania, found that magnesium supplementation as an adjunct to medication resulted in clinical improvement in seven patients, and that medication dosages were able to be lowered. Giannini and colleagues (2000), in a randomised controlled trial of 20 adults with manic symptoms, found that a combination of medication and magnesium supplementation resulted in a significant decrease in manic symptoms compared to a medication and placebo combination. Chouinard and colleagues (1990), found magnesium to have treatment benefits in seven of nine adults with rapid cycling BD.

Selenium is an essential trace mineral that has antioxidant properties, protecting cells from free radicals. Using a double-blind cross-over design, Benton and Cook (1991). found that selenium supplementation for five weeks, compared to placebo, was found to improve mood and decrease anxiety in healthy participants, especially those who had selenium-deficient diets to begin with (Benton & Cook, 1991).

A review by Kaplan and colleagues (2007) highlighted that 100 years of research examining single-nutrient interventions on psychiatric symptoms has provided some promising results, although modest. This is not surprising given that most diseases are multi-factorial (Mertz, 1994). In the field of physical illness, studying multiple nutrients together is more accepted (Mertz, 1994). There has been a growing body of research since 2000 on multi-ingredient micronutrient formulas for the treatment of psychiatric symptoms (Kaplan et al., 2007). This research will now be discussed.
1.6 Effects of multi-ingredient micronutrient interventions on psychiatric symptoms

A literature on multi-ingredient micronutrient formulas for mental health has more recently developed. This approach, based on the logic that nutrients work together in the brain and that humans require multiple nutrients, is gaining in popularity, particularly in the field of physical health (see review by (Kaplan, et al., 2007)). It has been argued that a broad-based micronutrient approach may be more effective than interventions consisting of only a single nutrient in the treatment of complex brain dysfunctions and complex psychiatric illness (Kaplan, et al., 2007). Almost two decades ago, a leading researcher in the field of nutrition, Walter Mertz, argued that the concept of “one-disease – one-nutrient” was outdated (Mertz, 1994). Humans require a mixture of nutrients and “designing dietary measures with only one nutrient in mind does not explore the full potential of the intervention; it may even introduce the risk of marginal imbalances and deficiencies” (Mertz, 1994 p. 1262). It has been proposed argued that the single ingredient approach is probably too narrow (Kaplan et al., 2007; Mertz, 1994). At present, there is no single nutrient that appears to show more therapeutic potential than all others (Kaplan, et al., 2007). Pauling (1995) stated that the “functioning of the brain is affected by the molecular concentrations of many substances that are normally present in the brain. The optimum concentrations of these substances for a person may differ greatly from the concentrations provided by his normal diet and genetic machinery. Biochemical and genetic arguments support the idea that orthomolecular therapy, the provision for the individual person of the optimum concentrations of important normal constituents of the brain, may be the preferred treatment for many mentally ill patients.” Research employing the multi-ingredient micronutrient approach will now be discussed.
1.6.1  Mood, Anxiety and Stress

Benton and colleagues (1995) conducted a double-blind RCT examining the impact of vitamin supplementation (nine vitamins) for a year on mood in a sample of 209 healthy adults. Females taking the vitamin supplement reported significantly better mental health at 12 months than those taking the placebo, as measured by the General Health Questionnaire (GHQ). However, in males there was no difference between groups. Furthermore, females taking the vitamin supplement reported themselves as significantly more composed at 12 months, than those taking placebo, as measured by the bipolar Profile of Mood States questionnaire (POMS). Again, there was no difference in males between the two groups. However, both males and females taking the vitamin supplement reported significantly higher agreeability at 12 months than those taking placebo (Benton, et al., 1995).

Carroll and colleagues (2000), in a double-blind RCT, investigated the effects of a multivitamin and mineral supplement (“Berocca”) on psychological well-being. The supplement includes vitamins B1, B2, B6, B12, C, niacin, pantothenic acid, biotin, folic acid, calcium, magnesium and zinc. Eighty healthy adult males, aged between 18 and 42 years, took either the micronutrient supplement or placebo, for 28 days. The micronutrient supplement resulted in statistically significant reductions in anxiety, as measured by the General Health Questionnaire (GHQ-12), the Hospital Anxiety and Depression Scale (HADS) and a 7-point rating of anxiety. The effect was robust across the different measures of anxiety. In addition, the micronutrient supplement was associated with a significant reduction in perceived stress, as measured by the Perceived Stress Scale (PSS). The group receiving the supplement also tended to report being less tired and more able to concentrate following treatment. In addition, participants endorsed more somatic symptoms following placebo than micronutrient treatment (Carroll, et al., 2000).

Schlebusch and colleagues (2000) conducted a double-blind RCT with 300 adults across two centres in South Africa with high stress levels, examining the effects of “Berocca Calmag”
(slightly different to Berocca i.e. no folic acid and zinc) on stress. Both groups demonstrated improvements on measures of stress; however, the degree of improvement was significantly greater in the micronutrient group than in the placebo group. More specifically, improvements were noted on the Hamilton Anxiety Rating Scale (HARS), the Psychological General Well-being schedule (PGWS), the Berocca Stress Index (BSI) and a visual analogue scale measuring patients’ subjective estimates of stress (Schlebusch, et al., 2000).

Kennedy and colleagues (2010) replicated the results of Carroll and colleagues (2000). In a double-blind RCT, “Berocca” was trialled for one month with 215 healthy males aged 30 to 55. Supplementation resulted in significant improvements in vigour (on the POMS), perceived stress (PSS), general mental health (GHQ-12). Furthermore, significant improvements in cognitive function were found with the micronutrients compared to placebo, on the serial 3’s subtractions task. In addition, the micronutrient group also rated themselves as less ‘mentally tired’ both before and after completing the cognitive test battery (Kennedy, et al., 2010).

Gosney and colleagues (2008) conducted an RCT examining the effect of selenium, vitamin C and folate on mood in 73 nursing home patients over the age of 60. In those with higher depression as measured by the Hospital Anxiety and Depression Scale (HADS) at baseline, there was a significant decrease in depression after eight weeks of micronutrient supplementation, compared to placebo. In addition, there was a significant increase in serum selenium levels (Gosney, et al., 2008).

1.6.2 Aggressive and antisocial behaviour

Schoenthaler and colleagues (1997), in a double-blind RCT, examined the effects of vitamin and mineral supplementation for three months on violence and other serious antisocial behaviour in 62 incarcerated juveniles aged 13 to 17 years. The supplement contained 12
vitamins and 11 minerals. There were significant differences between the active and placebo groups on both violent and non-violent rule violations. Total rule violations were reduced by 83 percent in the active group compared to 55 percent in the placebo group (Schoenthaler, et al., 1997).

Schoenthaler and Bier (2000) carried out a double-blind RCT of low-dose vitamin and mineral supplementation (18 ingredients) with 80 disruptive school children aged 6 to 12 years, investigating the effect on delinquency, as measured by school disciplinary records. The children included in the study had been disciplined at least once. The duration of the intervention was four months and children received two tablets each day. During the intervention, the group receiving the active tablets committed significantly fewer rule violations than the placebo group (47 percent lower mean rate of antisocial behaviour: threats/fighting, vandalism, disrespect, disorderly conduct, defiance, obscenities, refusal to work and endangering others; 1 versus 1.875 disciplinary actions). The authors argued that this study highlights the importance of correcting nutrient intake via supplementation for improving brain function and subsequently reducing antisocial behaviour (Schoenthaler & Bier, 2000).

Gesch and colleagues (2002) conducted a double-blind RCT of supplementation with vitamins, minerals and essential fatty acids (26 ingredients) in 231 young adult prisoners. The group receiving the nutritional supplement demonstrated a reduction from baseline in their rate of offending (disciplinary incidents) by 35.1 percent, whereas the group receiving placebo only showed a 6.7 percent reduction. Those receiving the nutritional supplement committed an average of 26 percent fewer offences than those receiving placebo (Gesch, et al., 2002).

Walsh, Glab and Haakenson (2004) conducted a case series of 207 children and adults aged 3 to 55 years, examining the impact of individualised formulas of vitamins, minerals and amino acids on externalising behaviour. The formulas were based on the individuals’ diagnosed imbalances. The outpatients had a prior diagnosis of ADHD, CD, ODD or other behaviour
disorder. Follow-up ranged from four to eight months. Following therapy, there were significant reductions in frequency of assaults and destructive behaviour, as measured by the Walsh-Isaacson Behavior Scale (WIBS). Of the assaultive patients that were compliant with the treatment regimen at follow-up, 58 percent achieved elimination of this behaviour. In addition, 53 percent of the compliant destructive patients achieved elimination of destructive behaviour (Walsh, et al., 2004).

Zaalberg and colleagues (2010) carried out an RCT examining the effects of nutritional supplementation on aggression, rule-breaking, and psychopathology among 221 young adult prisoners aged 18 to 25. The objective of the study was to investigate whether the findings of Gesch (2002) could be replicated in a different country with a comparable group of young adult offenders. The nutritional supplements included 25 vitamins and minerals and several fatty acids. A significant reduction was found in the number of reported incidents involving prisoners who took the supplements compared with those who received placebo. The experimental group demonstrated a 34 percent reduction, whereas the control group demonstrated a 14 percent increase. These incidents were documented accounts of observed behaviour perceived as disruptive or dangerous by prison staff and that is violating prison rules. This finding therefore has practical relevance (Zaalberg, et al., 2010). However, no significant differences were found on other measures including the Aggression Questionnaire (AQ), the Symptom CheckList-90 (SCL-90), the General Health Questionnaire-28 (GHQ-28) and the Social Dysfunction and Aggression Scale (SDAS), although there were trends toward improvement in the experimental group compared to the control group, on the AQ and GHQ-28 (Zaalberg, et al., 2010).
1.7 Literature on EmpowerPlus (EMP+)

The discussion above provided support for investigating the clinical benefit of a nutritional supplement, EMP+. It is a broad-based nutritional supplement consisting of 36 ingredients, including trace minerals (16), vitamins (14), amino acids (3) and antioxidants (3). See Appendix A for the ingredient list. David Hardy and Anthony Stephan formulated this supplement based on agricultural knowledge concerning the treatment of aggression in livestock. This nutritional supplement is now the most studied micronutrient supplement with 14 published studies to date. EMP+ has been examined for the treatment of mood instability in both adults and children. It has also been examined in the treatment of ADHD, OCD and Autistic Spectrum Disorder. The research on EMP+ will now be reviewed. It is important to note that the processing method of EMP+ changed in November 2002 in order to reduce the number of capsules needed to be taken from 32 to 15 capsules per day for the full adult dose. Therefore, research since 2002 has been on a newer formulation but with the same ingredients (Kaplan, et al., 2007).

1.7.1 Mood

Kaplan and colleagues (2001) investigated the therapeutic effects of EMP+ in a six-month open-label trial with 11 adults, aged 19-46, with Bipolar Disorder. Three additional participants dropped out of the study prematurely. The final sample consisted of 10 males and one female. Six met criteria for BD-I, four met criteria for BD-II and one for BD-NOS. Co-occurring diagnoses included OCD, dysthymia and ADHD. Participants were taking a mean of 2.7 medications at study entry. Three primary measures were employed: the Hamilton Depression Scale (HAM-D), the Brief Psychiatric Rating Scale (BPRS) and the YMRS. Participants took 32 pills daily, divided into four doses of eight pills. Participants were
monitored for a minimum of six months (range: 6-21 months). In intent to treat analyses (n=14), statistically significant reductions in both HAM-D and YMRS scores were demonstrated. In addition, there was a trend for lower scores on the BPRS. However, in the analysis of completers (n=11) statistically significant improvements from study entry to the most recent visit were demonstrated for depression (HAM-D), mania (YMRS) and general psychiatric status (BPRS). Effect sizes were large (>0.80) for each outcome measure. Mean symptom reduction was 55 percent for depression, 60 percent for general psychiatric status and 66 percent for mania. Of eight patients included in the analyses of responders, seven met criteria for responder status (at least a 20 percent reduction on all three outcome measures). There was also a significant decrease, greater than 50 percent, in mean number (1.0) of psychotropic medications. Of clinical importance, nausea was the only side-effect reported, and this was only temporary and occurred especially if patients did not take the pills with food. Patients reported that the supplement was easy to tolerate. As highlighted by the authors of the study, limitations of this study include lack of placebo control, lack of generalisation to women, and the concurrent use of psychiatric medications meaning it is impossible to attribute symptom changes to the micronutrients alone. Furthermore, the findings are limited by the open-label design. However, it is worthy to note that the majority of psychiatrists expected to see no benefit. The authors highlighted a strength of the study was that the final sample was unselected in that they were the first 11 patients with BD who were assessed systematically and followed for a minimum of six months (Kaplan, et al., 2001).

Popper (2001) reported a naturalistic A-B-A-C-B trial with a 10-year old with pediatric BD who displayed severe temper tantrums. The tantrums significantly improved after two days on EMP+ and irritability and outbursts were absent at five days. After two weeks, the supply of EMP+ had run out and within 48 hours of not taking the supplement, temper tantrums had
returned. The child then started on a similar supplement and showed moderate improvement but not nearly as great as the improvement associated with EMP+. Subsequently, the child began taking EMP+ again and the symptoms remitted completely; full stabilisation was achieved on the nutritional supplement without psychiatric medications and there were no adverse effects observed. Popper (2001), in his clinical practice, conducted additional trials of EMP+ among adults and adolescents with BD. Among the 22 patients, 19 responded positively to the supplement (Popper, 2001). Simmons (2002) reported using EMP+ to treat 19 adults with treatment-resistant BD. Of the 19 patients, 12 showed marked clinical improvement, three showed moderate improvement and one showed mild improvement. Thirteen patients were able to discontinue psychiatric medications after several weeks and remained stable on EMP+ alone (Simmons, 2002).

Kaplan and colleagues (2002), conducted naturalistic ABAB case studies of two children, both with mood lability and explosive rage, and found clinically significant improvements in mood and behaviour associated with the use of EMP+. The micronutrient formula was taken at a dose of 32 pills a day, divided into four doses of eight pills. The primary measures were a modified version of the Conner’s Parent Rating Scale (CPRS) and the Child Behavior Checklist (CBCL). Items on the CPRS were rated from 0-3 (0 = not at all, 1 = just a little, 2 = pretty much, 3 = very much), with the two items on mood lability and temper outbursts of primary importance. Parents rated their child’s behaviour daily using the CPRS.

The first case was an 8-year-old boy with atypical OCD (no discernible compulsions), ADHD, mood lability and explosive rage. His angry outbursts occurred at least twice daily during the year prior to the study. He also displayed depressive withdrawal. At baseline, he obtained T-scores greater than 70 on seven of the eight CBCL scales, and a mean score of 1.6 on both the CPRS mood lability and tantrums items (each item ranges from 0-3). In addition, to
assess the severity of his obsessions the Child Yale-Brown Obsessive Compulsive Scale (CY-BOCS) was administered, on which he obtained a score of 13. By day 15 of the first intervention, his family reported a reduction in frequency and especially duration of rage attacks and that his mood was generally calmer. By the end of week nine, there was a decrease in his obsessions (CY-BOCS: 5). Furthermore, at the end of week 16, his parents reported no residual symptoms and his mother described him as “wonderful”. The child reported that he could go all day without thinking about guns. All CBCL scale scores fell below the clinical cut-off score of 70 and he obtained a CY-BOCS score of 2. In addition, his average scores on mood lability and temper outbursts were both 1. His parents decided to stop the micronutrient treatment as they couldn’t clearly attribute the changes to the micronutrients. However, the family agreed for the boy to be monitored. By the end of week three off the micronutrients, the parents had noticed a return in his obsessive thought. At six weeks, three CBCL scales were clinically elevated. In addition, there was an increase on both items of the CPRS. The parents reported a significant clinical regression. The micronutrient formula was subsequently reintroduced. His parents reported improvements after two weeks. One year later, the boy was noted to have no behavioural or attentional difficulties. In addition, he obtained a CY-BOCS score of 1. There was a second treatment withdrawal and reinstatement in that approximately nine months after the last research interview, the family drifted away from using the micronutrients. However, he reportedly had a severe explosive rage about four to five weeks after stopping and therefore the micronutrients were reinstated (Kaplan, et al., 2002).

The second case was a 12-year-old boy who was diagnosed with Pervasive Developmental Disorder (PDD) with Asperger’s features at the age of four. In addition, he presented with severe ADHD, learning problems, irritability, mood problems and explosive outbursts. He obtained CPRS mean scores of 1.9 for mood lability and 1.7 for temper outbursts (scale ranges from 0-3). Furthermore, all eight CBCL scale scores were clinically elevated
His parents reported mood and behavioural improvements after three weeks on the micronutrients. Mean scores on the CPRS were 0.5 for mood lability and 0.1 for temper, very close to the scale minimum of 0 (*not at all problematic*). However, the child found it difficult to take the large number of pills and because of his new school placement the changes were not clearly attributable to the micronutrients. Therefore, the treatment was discontinued. After almost 3 weeks off the micronutrients, his CPRS scores increased back to baseline levels. The formula was subsequently reintroduced. After six weeks back on, all eight of the CBCL scale scores dropped to below the clinical cut-off of 70. In addition, his mean scores on the CPRS were 0.3 for mood lability and 0.2 for temper, again close to the scale minimum. It is important to note that he also took dextroamphetamine for his attentional difficulties. Improvements in mood and behaviour were maintained on a lower dose; 25 percent of full dose (Kaplan, et al., 2002).

It is worth noting that psychiatric medications were no longer needed for the first case and the two children and their parents did not report any adverse effects of the supplement. The authors noted that this nutritional intervention appealed to families who either were uncomfortable about using psychiatric medication or had experienced adverse side-effects of medications in the past (Kaplan, et al., 2002). It may also appeal to those who have not responded to medications or psychological interventions and therefore may be an alternative option they are willing to explore. The authors acknowledged that a limitation of this study was its open-label nature and was therefore influenced by expectancy effects and observer bias (Kaplan, et al., 2002).

Kaplan and colleagues (2004) conducted an open-label case series of nine children aged 8-15 clinically diagnosed with a mood, anxiety or behavioural disorder by the referring clinician. The original sample included seven boys and four girls with two of them dropping out.
prematurely. These children all had symptoms of irritability, mood swings and explosive rage in common. Outcome measures included the CBCL, the Youth Outcome Questionnaire (YOQ) and the YMRS. Children took 32 pills daily, divided into four doses of eight capsules. It was designed as an eight-week trial with weekly visits. However, due to summer vacations and illnesses etc., the actual number of weeks required to obtain eight follow-up visits ranged from 8 to 17 (mean = 13.6). Physicians were free to adjust psychiatric medications during the trial. In the intent to treat analyses, statistically significant reductions between baseline and the final visit was demonstrated for the YOQ and YMRS. However, the CBCL could not be analysed as the non-completers had only baseline scores available. Furthermore, in the completer analyses, there were statistically significant decreases on all of the CBCL scales (except somatic complaints). At study entry, at least two-thirds of the children scored in the clinical range on the Anxious/Depressed scale. However, no-one scored in the clinical range on this scale by the end of the trial. In addition, there were clinically significant improvements on the YOQ. A decrease of at least 13 points is considered to be clinically significant; scores for eight of the nine completers decreased by a minimum of 13 points (Kaplan, et al., 2004). The limited data on the YMRS also showed statistically significant improvements. The use of the YMRS was problematic in that some parents had difficulty in applying adult-oriented items to their children and chose to exclude it. Effect sizes on all outcome measures were large (greater than 0.80). Three completers who were taking psychiatric medications at study entry were still on medications at the end of the trial; however, their doses were lower. There were only minimal adverse effects, including transient nausea and vomiting in two patients and moderate agitation and excitability in two others (who were also on psychiatric medication). Limitations of this study include the open-label design (expectancy effects and observer bias) and that there was no independent confirmation of diagnosis, as noted by the authors (Kaplan, et al., 2004). However, the findings are consistent with earlier studies described above.
Frazier, Fristad and Arnold (2009) documented a case report of a 12-year-old boy with treatment-resistant BD-I with psychotic features, Generalised Anxiety Disorder (GAD) and OCD, successfully treated with EMP+ after six years of treatment with conventional medication. His psychiatric medications were slowly tapered and he was completely off all medications after 19 days on EMP+. The micronutrients were titrated up to the full dose of 15 capsules per day. His global functioning improved, interactions with peers were more appropriate, he remained calm and playful throughout the day, slept throughout the night, and was focussed and efficient doing schoolwork. Compulsions decreased and he no longer experienced hallucinations. His anxiety, impulsivity and fidgeting decreased. All symptoms of psychiatric disorders were fully remitted (Frazier, et al., 2009).

Gately and Kaplan (2009) conducted a large database analysis of adults with BD consuming EMP+. Self-report data were available from 682 adults with a reported diagnosis of BD. Included in the analyses were 358 adults; the others were excluded due to co-occurring diagnoses and providing data less than 60 times over a 180-day period. The use of EMP+ was associated with a 41 percent reduction from baseline in mean symptom severity at three months and an effect size of 0.78. These improvements were sustained at six months, with a 45 percent reduction from baseline and an effect size of 0.76. Both decreases were statistically significant when compared to baseline symptom severity. Reductions in symptom severity over the six months were found to be associated with increasing micronutrient dose and with reducing medication; 72 percent of the variance in symptom severity was accounted for by the micronutrient dose. Reducing medication use over the six months was associated with lower symptom severity (Gately & Kaplan, 2009).
Rucklidge, Gately and Kaplan (2010) conducted a database analysis of children and adolescents, aged 7 to 18, with Pediatric Bipolar Disorder (PBD) consuming the micronutrient formula, EMP+. Data were available for 120 children and adolescents whose parents reported a diagnosis of PBD; 24 per cent also were reported as having ADHD. Data were analysed from three to six months of micronutrient use, using Last Observation Carried Forward (LOCF). Parents tracked their child’s progress on a mood checklist, and for some, an ADHD checklist. AT LOCF, mean symptom severity of bipolar symptoms was 46 percent lower than baseline, producing an effect size of 0.78. Only 38 percent were still taking psychiatric medication, although at much lower levels, compared to 79 percent at baseline. In those with both PBD and ADHD, there was a 43 percent decline in bipolar symptoms and a 40 percent decline in ADHD symptoms. Similar findings were found for younger and older children as well as both sexes. However, as highlighted by the authors, there were some limitations of the study including the open label nature, lack of a control group and the inherent self-selection bias. In addition, all of the data were based on parent report with no corroborating reports. Still, these results are consistent with a growing body of research indicating that micronutrients appear to have therapeutic effects for children with PBD. This intervention has advantages in that there appeared to be minimal side-effects and safety has been established through monitoring of biochemistry, blood pressure, weight and haematology (Rucklidge, et al., 2010).

1.7.2 Obsessive Compulsive Disorder

Rucklidge (2009), using an ABAB design, found that EMP+ was successful in treating OCD in an 18-year old male after only partial response to cognitive-behavioural therapy. Therefore, he presented as a treatment-resistant and chronic case of OCD. In addition, he met criteria for Major Depressive Disorder prior to beginning the micronutrient supplement. At baseline, he obtained a score in the severe range on the Y-BOCS (24). He was mostly
experiencing obsessions. Outcome measures were selected to monitor treatment response over time: the Beck Depression Inventory-II (BDI-II), the Beck Anxiety Inventory (BAI), the Global Assessment of Functioning (GAF), the CBCL, and the Outcome Questionnaire (OQ). He titrated up over a one-week period to the full dose of 15 capsules per day, divided into three doses of five. At three weeks on the micronutrients, his mood had lifted and his anxiety had dropped markedly. His Y-BOCS score dropped to 12, the lowest it had been in over four years. He was followed every few weeks for two months. Outcome measures were repeated at eight weeks. Although his mood had improved, his BDI-II score was still relatively high (20). Clinically significant changes in anxiety were confirmed by his scores on the CBCL, BAI and the Y-BOCS. In addition, his OQ score had decreased into the range found in community samples. At the end of this eight-week period, he decided to discontinue treatment to determine what caused the change in his symptoms. However, he consented to be monitored during the withdrawal phase. At three weeks off, HE experienced a clinically significant increase in his obsessions, with a Y-BOCS score of 22 (moderate range). Outcome measures were repeated after eight weeks off the micronutrients, showing that his obsessions and anxiety had increased in severity, and his mood had dropped. He subsequently decided to resume the micronutrients. By four weeks back on, his Y-BOCS score of 10 indicated that his OCD symptoms were back in remission. Outcome measures were also repeated at eight weeks back on, indicating decreases in anxiety and obsessions and a lift in his mood although it still fell within a moderate range. However, he no longer met criteria for a major mood disorder. He was contacted six months later and he was still taking EMP+. He continued to be in remission with a Y-BOCS score of 10 and there were further improvements in his mood. It is important to note that no side-effects were reported while taking EMP+ (Rucklidge, 2009). In summary, his treatment response was replicated through an ABAB design, demonstrating on-off control of symptoms with the micronutrients.
1.7.3 Attention Deficit Hyperactivity Disorder

Rucklidge, Taylor and Whitehead (2011) carried out an 8-week open-label trial of EMP+ in 14 adults with both ADHD and SMD. Significant improvements were found across informants (self, observer and clinician) on measures of inattention, hyperactivity/impulsivity, mood, anxiety, stress and quality of life. All effect sizes were in the medium or large ranges. The means of mood and hyperactivity/impulsivity were normalised; however, the mean of inattention remained in the clinical range. Follow-up data confirmed maintenance of changes or further improvements for those who continued to take the micronutrient supplement after the open-label trial. At a 2-month follow-up, means across all primary outcome measures were lower for those who stayed on compared with those who decided to stop taking EMP+ (Rucklidge, et al., 2011). A double-blind RCT examining the effects of EMP+ in a population of adults with ADHD and SMD is currently underway at the University of Canterbury.

1.7.4 Autistic Spectrum Disorder

Mehl-Madrona and colleagues (2010) carried out a naturalistic case-control study comparing micronutrients to standard medication management in 88 individuals with Autistic Spectrum Disorder (ASD). Forty-four families asked for treatment without pharmaceuticals and therefore were assigned to the micronutrient group. Their records were matched with those of 44 similar individuals whose families wanted conventional treatment and therefore comprised the medication group. Both groups demonstrated improvements on the Childhood Autism Rating Scale (CARS). With the exception of the micronutrient group showing a statistically significant lower activity level on the CARS, no other group differences were found. Both groups also showed improvements on the Childhood Psychiatric Rating Scale. Statistically significant group differences were found for several characteristics; the micronutrient group displayed less social
withdrawal, less angry affect and better spontaneity with the examiner. In addition, both groups also demonstrated statistically significant decreases in total Aberrant Behavior Checklist scores. However, the micronutrient group showed a statistically significant greater improvement. More specifically, the micronutrient group displayed lower irritability and hyperactivity which were both statistically significant. Furthermore, intensity of self-injurious behavior was lower in the micronutrient group at the end of the study although there was no change in frequency. In addition, improvement on the Clinical Global Impressions scale was greater for the micronutrient group. Furthermore, the micronutrient group had less adverse events and less weight gain than the medication group. In summary, comparable symptom management with both micronutrients and pharmaceuticals in children and young adults with ASD was found in this study. No advantage was detected for pharmaceutical management in terms of improving any type of symptom. In contrast, micronutrients resulted in several statistically significant advantages. However, as highlighted by the authors, the advantages of medication management were insurance coverage, fewer pills and less frequent dosing. Limitations of this study included the potential bias of the clinician who was not blind to the treatment conditions (Mehl-Madrona, et al., 2010).

As is evident, there are some promising results of EMP+ in the treatment of a range of psychiatric disorders; however, the studies are few. Further research needs to be conducted on the effects of this micronutrient formula across different age groups and different psychiatric conditions. The positive results from the studies described above provided the impetus to study the impact micronutrients may have on adolescents with severe mood dysregulation and co-occurring psychiatric conditions. The present study investigated the effects of EMP+ on mood and functioning in adolescents aged 16 to 21, using an ABAB design. Individuals were also followed for a much longer period of time than was typical in previous studies and the majority
of pharmacological trials. It was hypothesised that EMP+ would be associated with improvements in mood and functioning in these adolescents. A pattern of reversal and replication of treatment response was expected.

1.8 Hypotheses

- The micronutrient formula would not be associated with significant side-effects, if present, only minor and transitory
- Participants would be able to swallow 15 pills a day
- The micronutrient formula would be associated with improvements in mood
- The micronutrient formula would be associated with improvements in general functioning, as well as anger, anxiety, stress and ADHD symptoms (if relevant)
- Withdrawal of the micronutrient formula would be associated with deterioration in mood, general functioning, and other psychiatric symptoms, with a return to baseline, or near baseline, symptom severity
- Reintroduction of the micronutrient formula would again be associated with improvements in mood and functioning, revealing a replication of the first phase
- Improvements would be maintained over time while on EMP+
2. Method

2.1 Participants

Nine adolescents between the ages of 16 and 21 with SMD were recruited for this treatment study. Co-occurring disorders were also present, including ADHD, Conduct Disorder, PTSD, Social Phobia, Panic Disorder and substance abuse/dependence. Referral sources included the Canterbury District Health Board (CDHB), General Practitioners and advertising. One case initially self-referred to a RCT on EMP+; however, he was deemed more suitable for the present study. Nine adolescents, recruited for the study were given information about the study and were invited to participate in the initial screening for the study.

2.1.1 Diagnostic Protocol for Psychiatric Disorders

Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL; (Kaufman et al., 1997). The K-SADS-PL is a semi-structured diagnostic interview that assesses broadly across all domains of functioning. It is designed to assess current and lifetime history of psychiatric disorders, in children and adolescents aged 6 to 18, according to DSM-III-R and DSM-IV criteria, and is administered by a trained clinician. Probes and objective criteria are provided to rate individual symptoms. The K-SADS-PL is administered by interviewing the parent(s), the child, and finally achieving summary ratings which include all sources of information. Diagnoses are generated by synthesising parent and child data. Five diagnostic supplements are included (affective disorders, psychotic disorders, anxiety disorders, behavioural disorders, and substance abuse and other disorders) which are administered depending on the results of the Screen Interview. The Screen Interview surveys the
primary symptoms of the different diagnoses assessed in the K-SADS-PL. It has been widely used in research. High inter-rater reliability (98%) has been found. In addition, excellent test-retest reliability has also been found (Kaufman, et al., 1997).

Washington University in the St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia mood section (WASH-U-KSADS; (Geller et al., 2001)). This section was administered to assess for Bipolar Disorder in children and adolescents aged 6 to 18. See K-SADS-PL above.

Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version (SCID-I; (First, Spitzer, Gibbon, & Williams, 2002)). The SCID-I is a semi-structured diagnostic interview based on DSM-IV Axis I criteria. It is used to screen for lifetime and current psychiatric disorders and is administered by a trained clinician. It is most appropriate for use with adults aged 18 and over. Screening questions endorsed by participants were explored in more depth. The SCID-I covers mood, psychotic, substance use, anxiety, somatoform, eating and adjustment disorders.

Conners’ Adult ADHD Diagnostic Interview for DSM-IV (CAADID; (Epstein, Johnson, & Conners, 2001)). This semi-structured interview is used to assist in the process of diagnosing ADHD in adults aged 18 and older. The CAADID assesses each of the nine ADHD inattentive symptoms and nine hyperactive/impulsive symptoms across both childhood and adulthood. Information is also gathered on age of onset, pervasiveness and level of impairment for any ADHD symptom that is indicated. Using the CAADID responses, participants were then classified according to ADHD subtype: Combined Type, Predominantly Inattentive Type or
Predominantly Hyperactive/Impulsive Type. This interview took approximately 60 minutes to complete and was administered to the ADHD participants only.

2.1.2 Inclusion/Exclusion Criteria

It was required that participants have some form of mood dysregulation, whether it was depression, Bipolar Disorder or chronic irritability. Other co-occurring psychiatric disorders were not excluded. Therefore, the participants are a broad sample of adolescents with complex presenting problems. It was required that participants were medication-free for at least four weeks.

Participants were excluded from the study for any of the following reasons:

1) neurological disorder (e.g., epilepsy, multiple sclerosis, narcolepsy),

2) pregnancy or breastfeeding (pregnancy testing occurred at baseline and monthly thereafter),

3) evidence of untreated or unstable thyroid disease, or abnormality of mineral metabolism (testing occurred at baseline),

4) if they had taken an antibiotic in the previous 6 weeks. If an antibiotic was started during the course of the trial, the patient was withdrawn from the study,

5) evidence of substance dependence within the previous month,

6) any subject judged clinically to be at current serious risk for suicide, self-harm or violence.

Participants were allowed to continue other forms of psychological therapies and nutrient supplements if dose and intensity did not change.
2.1.3 Final Sample

Three participants (KT, TJ and AP) completed the entire trial. KT, a 21-year-old female, met diagnostic criteria for BD-II, ADHD Combined Type, Social Phobia and Panic Disorder with Agoraphobia. TJ, a 20-year-old male, met diagnostic criteria for Major Depressive Disorder, ADHD Combined Type, Specific Phobia, Panic Disorder with Agoraphobia, Cannabis Abuse and Alcohol Abuse. AP, a 20-year-old female, presented with a Major Depressive Disorder and PTSD.

Two participants (JB and BT) completed the first open-label phase but chose to withdraw from the study following this phase. JB, a 16-year-old female, met diagnostic criteria for Bipolar Disorder NOS, ADHD Combined Type, Social Phobia, GAD and Conduct Disorder. JB was in a youth justice facility at the time of assessment. BT, a 21-year-old male, met criteria for Major Depressive Disorder, ADHD Combined Type, Social Phobia, OCD and Specific Phobia.

2.1.4 Drop-outs and Exclusions

Two participants (CJ and PM) dropped out after two to three weeks of taking the micronutrients. Further, two participants (HL and JS) completed part of the baseline assessments only. CJ, a 17-year-old female, met with the researchers to discuss the study. A K-SADS-PL semi-structured interview confirmed the presence of Major Depressive Disorder. There was evidence of irritable mood; however, not elevated mood. The interview and assessment measures indicated that CJ had a mixed presentation of mood symptoms, consistent with SMD. CJ reported frequently feeling low since the age of 11. CJ overdosed on Panadol on one occasion and spent some time in residential care following this incident. She also has a history of self-harm, more specifically cutting. CJ reported trying a number of antidepressant medications in the past; however, she experienced severe side-effects and did not notice any improvement in her
symptoms. CJ also met criteria for Social Phobia, GAD and OCD. Some Inattentive symptoms of ADHD were present; however, these were sub-threshold and she did not meet criteria for ADHD. There was a flavour of oppositional behaviour, particularly based on CJ’s mother’s perspective. CJ has a history of substance use. She met criteria for both alcohol and cannabis (smoking daily in the past) dependence, as well as solvent abuse (butane: 2 cans a day for 8 months). However, she denied any current use of alcohol or drugs. She stopped smoking cigarettes four to five months prior to the assessment. CJ reported motor tics including eye blinking, head jerking and arm movements; however, these have apparently improved over time. CJ also struggled with poor eating. She described some fears of becoming obese and reported binge eating episodes once every few months following extended periods of not eating.

CJ tried taking the micronutrients for a couple of weeks; however, she found it very difficult to swallow the pills. We provided her with information regarding various techniques that can help with swallowing pills but she struggled to follow through with the suggestions. A session was carried out with CJ which aimed to help her overcome the fear of swallowing pills. Different techniques were suggested; for example, where the pill is placed in the mouth and the position of the neck. However, CJ would not swallow the pills in front of us and we were therefore limited in the extent to which we could assist her. She experienced a great deal of anxiety surrounding swallowing the pills (i.e. feeling the pill go down her throat). Because of these difficulties with swallowing the pills, CJ was offered the micronutrients in a powder form. CJ failed to show up to several scheduled appointments following getting her started on the powder. Apparently she did not feel well after taking the powder. This may have been due to taking the powder on an empty stomach. However, she chose to withdraw from the trial as she reportedly could not get up to the amount she thought she was supposed to be taking. She likely only took a few pills in total.
PM, a 21-year-old male, was referred to the study in June 2010 by his parents who had read about the research in The Press. Based on the CAADID, PM met DSM-IV criteria for ADHD, combined type. Based on his responses to SCID-I questions, he met criteria for Major Depressive Disorder, GAD, Cannabis Abuse and Alcohol Abuse. He also experiences a great deal of irritability, reporting that he gets “irrationally angry”. He expressed getting irritable any time he is with his father or brother and reported an incident in which he called a bouncer a “maggot”. He reported a recent incident in which he almost got in a fight in town. PM reported threatening a guy; however, the bouncers intervened. PM has been on various medications in the past including methylphenidate, fluoxetine and citalopram. He reported that fluoxetine did not do anything for him and that citalopram levelled him too much and described feeling like he was in a day-dream, “default blur” and felt like it was not him. PM described that methylphenidate resulted in him changing from an “extraverted maniac to introverted”. PM started taking the micronutrients and stayed on for about three weeks, although he did miss a number of doses (approximately 20 percent of doses over a three-week period). However, he decided to withdraw from the trial as he believed the pills did not do anything for him and did not see the point in coming in for regular appointments when there was no change. PM was encouraged to be patient and to give it some more time to see whether the micronutrients could make a difference for him or not; however, he dropped out of the trial.

HL, a 16-year-old female, was referred to us by her mother after seeing an advertisement for the study. She reported experiencing low mood for the past few years, four to five days a week, for two to three hours a day. This low mood was slightly worse during her menstrual cycle. She reported locking herself in her room and slamming the door. There was no evidence of mania. She had tried herbal supplements; however, she did not notice any remarkable improvement. A baseline assessment was carried out with HL (psychiatric interview, questionnaires). However, she did not particularly want to get blood tests done and did not want
her teacher completing any questionnaires. As blood work is required by the study protocol in order to assess for exclusion criteria, we could not proceed with HL.

JS, an 18-year-old female, was referred to us by a psychiatrist within the in-patient services as she had refused to accept conventional treatments for her bipolar symptoms. The study was discussed with JS over several meetings following her discharge from the hospital. During these meetings, JS made it very clear that she only wanted a treatment that was “natural”. Although there were some signs of elevated mood and there was some evidence of tangential thoughts and flight of ideas, JS was coherent and able to discuss the study intelligently. She showed an ability to weigh the pros and cons and come to an informed decision about her health care. She took the information sheet away with her and was informed that if she wanted to be in the trial she should contact the investigators. After several days, JS made contact confirming that she wanted to participate in the trial. However, at this point, concerns were raised from the CDHB regarding her ability to consent and as such, the CDHB refused to provide her with ongoing care should she participate in the trial. In order to avoid compromising her health care, and despite her refusal of conventional treatments, she could not be accepted into the trial.

2.2 Measures

2.2.1 Measurement of Demographic Variables

*History Questionnaire:* This questionnaire was used to assess for demographic variables. Participants were provided categories to select the following: ethnicity, marital status, home situation, highest educational qualification and annual income before tax. Participants were also asked to list their occupation and partner’s occupation if applicable. In addition, they were asked to list any medications they were currently prescribed or medications taken in the past for mental
health issue. In addition, they were asked about ever having a head injury with loss of consciousness, ever taking an antibiotic and ever been diagnosed with a yeast infection. See Appendix A.

New Zealand Socioeconomic Index of Occupational Status (NZSEI; (Davis, McLeod, Ransom, & Ongley, 1997)). The NZSEI is based on 1991 New Zealand census data and scores range from 10 and 90 (with higher scores indicating higher SES). This scale provides an estimate of socioeconomic status (SES) based on the individual’s occupational level.

2.2.2 Self-Rated Dependent Measures

Outcome Questionnaire (OQ; (Umphress, Lambert, Smart, Barlow, & Clouse, 1997)). The OQ is a 64-item self-report measure of treatment progress and outcome for adults (18+) receiving mental health intervention. It was designed to be repeatedly administered during the course of treatment. The timeframe used is a week. It attempts to measure a person’s subjective experience in addition to the way he or she functions in the world. The OQ measures functioning in three domains: Symptom Distress (SD), Interpersonal Relations (IR), and Social Role (SR). These domains of functioning cover how the person feels inside, how he or she is getting along with significant others, and how he or she is doing in important life tasks, such as work. The SD subscale is heavily loaded for depression and anxiety and also includes items on substance abuse. An example of an item from the SD domain is “I feel no interest in things”. The IR subscale includes items attempting to measure friction, conflict, isolation, inadequacy and withdrawal in interpersonal relationships. An example from the IR domain is “I have trouble getting along with friends and close acquaintances”. The SR subscale focuses on the person’s level of dissatisfaction, conflict, distress and inadequacy in tasks related to their employment, family
roles and leisure activities. An example from the SR domain is “I feel stressed at work/school”. The OQ takes approximately five minutes to complete. Each item is scored on a 5-point Likert scale (0-4), ranging from Never to Almost Always. Nine items are reverse-scored. Items are added to provide three individual subscale scores as well as a total score. The total score ranges from 0-180. The higher the score, the more disturbed the individual. The SD score ranges from 0-100, the IR score from 0-44 and the SR score from 0-36. There are four critical items, one related to suicide, two related to drug/alcohol abuse and one related to work violence. The OQ allows the clinician to compare the individual's behavior during treatment to normed samples of inpatient populations, outpatient populations, and a large untreated community population and a total score of 63 is typically used as a cut-off for identifying individuals at high risk for psychiatric problems (36 for SD, 15 for IR and 12 for SR). It enables clinicians and researchers to assess functional level and change over time. Reliable Change Index scores are 14 for the total OQ score, 10 for SD, 8 for IR and 7 for SR. The OQ has strong psychometric properties. In terms of reliability, internal consistency of the total score was found to be 0.93 in a patient sample. For each of the subscales, internal consistency was 0.91 for SD, 0.74 for IR and 0.71 for SR. Test-retest reliability for the total score was 0.84 in a student sample (0.78 for SD, 0.80 for IR and 0.82 for SR). Good concurrent validity has been found across three patient samples (college counselling centre, outpatient clinic and inpatient) with significant positive correlations between the OQ and Symptoms Checklist 90 R, Social Adjustment Scale and the Inventory of Interpersonal Problems (Umphress, et al., 1997). In terms of construct validity, scores for patients after seven therapy sessions were significantly lower than their baseline scores (67.18 vs 84.65). Therefore, the OQ is sensitive to change. Significant differences have also been found between clinical and non-clinical samples, providing further support for construct validity (Lambert et al., 2004).
Depression Anxiety Stress Scale (DASS; (Lovibond & Lovibond, 1995)): The DASS is a 42-item self-report questionnaire designed to measure current severity of depression, anxiety and stress. The DASS can be used with children and adolescents as young as 14. Each of the three DASS scales contains 14 items, divided into subscales of two to five items with similar content. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety and subjective experience of anxious affect. The Stress scale assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive and impatient. Examples of items include “I couldn’t seem to experience any positive feeling at all” (Depression), “I had a feeling of faintness” (Anxiety), and “I found myself getting upset by quite trivial things” (Stress). Items are rated on a 4-point Likert scale that reflects severity/frequency of each state over the past week, ranging from did not apply to me at all (0) to applied to me very much, or most of the time (3). Scores for Depression, Anxiety and Stress are calculated by summing the scores for the relevant items. Cut-offs have been provided to indicate mild, moderate or severe problems in each area; anything below 13 (for depression), 10 (for anxiety) and 18 (for stress) are considered within the normal to mild range. The moderate ranges are 13-20 for Depression, 10-14 for Anxiety and 18-25 for Stress. Any scores above these fall in the severe and extremely severe ranges. The DASS has demonstrated high internal consistency with Cronbach’s alphas of 0.84 for Anxiety, 0.90 for Stress and 0.91 for Depression in the normative sample. It is a useful measure when assessing changes in depression, anxiety and stress over time (Lovibond & Lovibond, 1995).

Novaco Anger Scale and Provocation Inventory (NAS-PI; (Novaco, 2003)): The NAS-PI is a comprehensive self-report measure of anger. It assesses how an individual experiences anger and identifies the type of situations that provoke anger for that individual. It is suitable for use with
children and adolescents aged 9 to 18 as well as adults (19+). It is a two-part measure. The Novaco Anger Scale (NAS) consists of 60 items that make up four subscales: Cognitive, Arousal, Behavioural and Anger Regulation. A total NAS score is also obtained. NAS items are rated on a 3-point Likert scale, ranging from *Never True* (1) to *Always True* (3). An example of an item on the Cognitive subscale is “Once something makes me angry, I keep thinking about it”. An example from the Arousal subscale is “My muscles feel tight and wound-up”. An example from the Behavioural subscale is “I feel like smashing things” and an example of an item from the Regulation subscale is “If I feel myself getting angry, I can calm myself down”. The Provocation Inventory (PI) consists of 25 items reflecting disrespectful treatment, unfairness, frustration, annoying traits of others and irritation. A total PI score is obtained; there are no PI subscale scores. PI items are rated on a 4-point Likert scale, ranging from *Not at all angry* (1) to *Very angry* (4). An example of an item from the PI is “Being criticized in front of other people for something that you have done”. The NAS-PI also has an Inconsistency Index which identifies inconsistent responding, based on 16 item pairs. T-scores and percentiles are provided. T-scores of 65 or higher indicate clinical elevations. It is a useful tool for assessing treatment change. The NAS-PI has demonstrated good test-retest reliability (median retest correlation of 0.78 in the standardisation sample) and excellent internal consistency (0.94 for NAS total score and 0.95 for PI total; (Novaco, 2003). In terms of concurrent validity, high correlations have been found between the NAS Total and the total score on the Aggression Questionnaire (Novaco, 2003). The NAS-PI is a useful tool for assessing therapeutic change (Novaco, 2003).

*Conners’ Adult ADHD Rating Scales - Self-Report: Long Version* (CAARS-S:L; (Conners, Erhardt, & Sparrow, 1999)). The CAARS-S:L was used as a measure of ADHD symptom severity. It has 66 items and 9 subscales. These are as follows: inattentive and memory
problems, hyperactivity and restlessness, impulsivity and emotional lability and problems with self-concept, three DSM-IV subscales for inattention, hyperactivity/impulsivity and combined inattention and hyperactivity/impulsivity, an ADHD Index and an Inconsistency Index. Each question was rated on a 4-point scale from not at all/never (0) to very much, very frequently (3). All raw scores can be converted to T-scores based on age and gender. The scale consists of a self-rating form and an observer form that is completed by an observer familiar with the adults’ behaviors. T-scores greater than 65 reflect clinical elevations. This measure was only used with those who met criteria for ADHD. It takes about 10 minutes to complete. Median test-retest reliability has been found to be .89 and internal consistency (Cronbach Alphas) ranging from .86 to .92 (Conners, et al., 1999).

2.2.3 Clinician-Rated Dependent Measures

Montgomery-Asberg Depression Rating Scale (MADRS; (Montgomery & Asberg, 1979)): The MADRS was designed to be used in patients with major depressive disorder to measure the overall severity of depressive symptoms over the past week. It is useful in evaluating changes in symptom severity over time. It is a 10-item measure that uses a likert scale of 0-6. The ratings are based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. It takes about 10-15 minutes to administer. A total score is obtained, which ranges from 0 to 60. The 10 items are as follows: apparent sadness, reported sadness, inner tension, reduced or increased sleep, reduced or increased appetite, concentration difficulties, lassitude, inability to feel, pessimistic thought and suicidal thoughts. The MADRS has acceptable reliability that is comparable to other clinician-rated depression scales. In terms of internal consistency, correlations between each item and the remaining items were found to range from 0.12 (reduced appetite) to 0.84 (apparent sadness)
Joint reliability for the total score ranged from 0.76 to 0.95 across several studies ((Davidson, Turnbull, Strickland, Miller, & Graves, 1986); (Montgomery & Asberg, 1979)). In terms of validity, a study found that all symptoms of the MADRS were present in 70 percent of patients with major depressive disorder (Davidson, et al., 1986). The MADRS is widely used in psychopharmacology research. The scale is easy to administer and does not require any special training. Hawley and colleagues (2002) suggests that a score of 10 or below on the MADRS indicates remission.

*Young Mania Rating Scale* (YMRS; (R. C. Young, Biggs, Ziegler, & Meyer, 1978)): The YMRS is an 11-item measure of the severity of manic symptoms. It is useful when assessing the effect of a treatment on the severity of mania over time as it is sensitive to change. Seven items are ranked 0 to 4 and have descriptors associated with each severity level. Four items are scored 0 to 8 have descriptors for every other increment. These items are given twice the range to compensate for the poor cooperation seen in severely ill patients. The 11 items are as follows: elevated mood, increased motor activity energy, sexual interest, sleep, irritability, speech (rate and amount), language-thought disorder, content, disruptive-aggressive behaviour, appearance and insight. A total score is obtained that ranges from 0 to 60. The YMRS is designed to be administered by clinicians. Average scores on the YMRS have been found to be 13 for minimal severity, 20 for mild severity, 26 for moderate and 38 for severe illness. However, these need to be viewed cautiously as they are based on a small sample (R. C. Young, et al., 1978). Correlations between each individual item and the total score have been found to range from 0.41 (appearance) to 0.85 (language and thought disorder) (R. C. Young, et al., 1978). Joint reliability for total scores was 0.93 in the same study (R. C. Young, et al., 1978). In terms of validity, one study found a correlation of 0.88 between the YMRS and a global mania rating.
scale, 0.77 with the Bech-Rafaelsen Mania Scale, and 0.89 with the Pettersson Mania Scale (Rush, et al., 2008).

**Global Assessment of Functioning (GAF) Scale** (Association, 2000) The GAF is a numeric scale that ranges from 1 (most impaired) to 100 (healthiest). It is widely used by mental health clinicians and doctors to rate the general functioning of adults. The GAF is on Axis V of the DSM-IV-TR. A score is obtained by rating either symptom severity or level of functioning. Anchors at 10-point intervals include descriptors of psychopathology and functioning. For example, a score falling within the 41-50 range reflects “Serious symptoms (e.g. suicidal ideation, severe obsessional rituals, frequent shoplifting) or any serious impairment in social, occupational, or school functioning (e.g. no friends, unable to keep a job”. A higher score represents less severe symptomatology or a better level of functioning.

**Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) Scales** (Spearing, Post, Leverich, Brandt, & Nolen, 1997). The CGI severity and improvement were assessed separately for depression, mania, and ADHD symptoms. The score for the CGI-S ranges from 1 (normal, not ill) to 7 (among the most extremely ill patients). The score for the CGI-I ranges from 1 (very much improved) to 7 (very much worse).

**Children’s Global Assessment Scale (C-GAS; (Shaffer et al., 1983)).** The C-GAS is a global measure of social and psychiatric functioning for children 4 to 16 years of age. It uses a numeric scale of 1-100. Anchors at 10-point intervals include descriptors of functioning and psychopathology. The single numerical score representing severity of disturbance ranges from 1 (most impaired) to 100 (healthiest). The C-GAS is one of the most widely used measures of overall severity of disturbance in children. It is based on an adaptation of the GAF for adults,
with anchor points that are especially relevant for children. It can be used to track treatment change. Joint reliability has been found to be high in research settings (0.83-091). Test-retest reliability has been found to be around 0.85 (Rush, et al., 2008).

Range of Impaired Functioning Tool (LIFE-RIFT; (Leon et al., 1999)) The LIFE-RIFT is a brief assessment tool used to explore functional impairment generally over the previous week in four domains: work, interpersonal relations (past month), recreation and global satisfaction. The interviewer asks questions guided by the behavioural anchors provided for each item in order to obtain the information needed to make the rating. The LIFE-RIFT score is a sum of four items. The ‘work’ and ‘interpersonal’ items each represent the maximum (most impaired) value among multiple items assessing the domain. The higher the score, the greater the impairment. It has been shown to be both reliable and valid. Internal consistency has found to be 0.82 at six months and inter-rater reliability was found to be 0.94 (Leon, 1999). The LIFE-RIFT was strongly negatively associated with the Global Assessment Scale (GAS), consistent with expectations as a high GAS score represents better functioning and less severe symptomatology (Leon, et al., 1999). It has been used in clinical trials of patients with bipolar disorder (Morris et al., 2005).

Conners’ Adult ADHD Rating Scales - Observer: Screening Version (CAARS-O:SV). The observer screening version has 30 items and three DSM-IV ADHD symptom subscales (Inattentive, Hyperactive-Impulsive and Total ADHD symptoms) and an ADHD Index. This was clinician-administered. It has excellent psychometric properties (Conners et al., 1999).

2.2.4 Observer-Rated Dependent Measures
Conners’ Adult ADHD Rating Scales – Observer: Long Version (CAARS-O:L): This is the observer version of the CAARS-S:L above. See CAARS-S:L for more detail. It has sound psychometric properties like the CAARS-S:L.

See Appendix B for demographic and outcome measures.

2.3 Design and Procedure

All study procedures were approved by both the University of Canterbury and Health and Disability Ethics Committees. All participants were given an information sheet about the study and signed consent forms after being informed about the experimental nature of the treatment. They were also informed of other treatments available in the community. Participants were not encouraged to come off a conventional treatment that was working in order to participate in this trial. Individuals who were referred to the study or who made contact regarding the study first underwent a screening either by phone or a meeting at the Department of Psychology, University of Canterbury. The purpose of this screening was to determine whether the individual was suitable for the trial. Those individuals who met the inclusion/exclusion criteria were informed of the study protocol and invited to participate in the trial. They were given an information sheet to take away with them to read. They were given time to consider the decision to take part in the trial and were to contact the primary investigator when a decision had been made. Informed consent was obtained from those who wished to take part in the trial. They were informed that they were able to withdraw from the trial at any stage. See Appendix C for the information sheet and consent form.

Adolescents who consented to take part in this trial underwent further assessment involving medical and psychiatric history. The participants underwent an in-depth interview
using the K-SADS-PL (Kaufman, et al., 1997) in combination with the mood section of the WASH-U-KSADS (Geller, et al., 2001) for those under the age of 18, or the SCID-I (First, Spitzer, Gibbon, & Williams, 2002) for those aged 18 and over, as well as the CAADID if ADHD was suspected. Where possible for the younger participants, a parent/guardian was interviewed separately. All clinical interviews were conducted by a clinical psychologist or a senior graduate student. All cases were discussed with a senior clinical psychologist.

Prior to starting the micronutrients, baseline hematological and biochemistry screening was completed including testing of: thyroid function, serum lipids, prolactin and glucose, blood clotting, iron, magnesium, and copper levels, urinalysis, urine drug screen and a pregnancy test (in females). Levels of vitamin B12, vitamin D and folate were also assessed. All lab results were reviewed by a psychiatrist or physician. Where possible, this blood screening was repeated post 8-10 weeks of intervention (it was repeated post 3 months of the second open label phase for one participant, and one participant withdrew before repeating the blood work). This screening was carried out to ensure that all systems were functioning normally and to assess for any abnormal effects of the micronutrients. File reviews (medical records i.e. psychiatric history, medications taken) were conducted with participant consent. As well as the psychiatric interview and blood work, participants also completed several questionnaires (DASS, OQ, NAS-PI and CAARS if relevant) to get a baseline level of severity of psychiatric symptoms. Interviewer measures (MADRS, YMRS, GAF, CGI’s, LIFE-RIFT, and for those diagnosed with ADHD, the CAARS observer screen) were administered at baseline before they started on the micronutrients.

The baseline assessment was followed by an open-label trial with EMP+ for an 8-10 week period. The ingredients of EMP+ are included in Appendix B. During the open-label trial, progress was monitored using outcome measures at regular intervals. During the trial, the participants met weekly or fortnightly with one of the primary investigators. At these
appointments, the participant’s physical and mental health were reviewed and a variety of measures (MADRS, YMRS, GAF, CGI’s) were administered in order to assess the participant’s overall functioning as well as specific problems identified during the clinical interview. Participants’ compliance was also assessed by asking if they were taking the full dose every day and whether they had missed any doses. Side-effects and medical problems were monitored at these regular appointments. Furthermore, weekly/fortnightly consumption of alcohol, cigarettes, cannabis, and caffeine was also tracked through self-report. See weekly visit form in Appendix D. Capsules were dispensed weekly/fortnightly. They were given a pill container so that daily doses could be divided up. It also meant it was easy for them to take the required number of pills to work or wherever they were going for the day. To begin with, participants were asked to take five capsules a day divided into three doses (2, 2, 1) and increase to 10 capsules a day after three days, divided into three doses (4, 3, 3). If possible, they increased to the full dose of 15 capsules a day on the seventh day, preferably divided into 3 doses of 5 capsules and always taken with plenty of food and water. If participants were unable to swallow the capsules, the supplement was available in a powder form (one participant had difficulty swallowing pills and opted for this option but subsequently withdrew from the trial). Participants were offered text reminders to their cell phones to assist with remembering to take the pills. Three participants opted for the text reminders.

At the completion of the 8-week open-label trial (10 weeks for three participants), participants repeated the battery of questionnaires that were administered at baseline to assess for any change in severity of symptoms. Three participants repeated the blood work (one repeated later in the trial and one withdrew from the trial). Participants then underwent an 8-10 week washout phase. If there was a significant relapse in symptoms during this phase, the extended trial would be reintroduced earlier. Participants were again monitored weekly or fortnightly
during this washout phase, in the same way as the open label phase. All outcome measures were administered again at the end of this washout phase. After this phase, all participants, regardless of their response to the supplement in the 8-week open-label trial, were offered up to 24 weeks of extended open-label trial with EMP+. This extended period provided an opportunity to assess the effects of the formula over a much longer period of time than is typically used in pharmacological trials. Again, monitoring of side effects and response to EMP+ occurred regularly throughout this phase. However, the intervals extended to approximately monthly as participants progressed through this phase. Outcome measures were repeated again after two or three months as well as 6 months on EMP+. A psychiatric interview was repeated at the completion of the trial.

Participants were encouraged to avoid/limit their consumption of alcohol, marijuana, caffeine, nicotine and street drugs throughout the trial as these substances may decrease the potential benefits of the micronutrient supplement. However, participants were asked to estimate their use of these substances at the regular appointments. Participants were also asked not to try any alternative medicines while involved in the trial. Participants were informed that if they needed to go on an oral antibiotic or antifungal drug at any point during the trial, they would have to withdraw from the study for the duration of the course of the drug. This is because antibiotic and antifungal drugs appear to interfere with the absorption of nutrients.

The clinical interviews (baseline and post-treatment) and weekly/fortnightly appointments were conducted at the University of Canterbury, within the Department of Psychology. Results of the testing were shared with the participants as well as the referring clinician(s)/service. At each visit, the participants were given a 10-dollar petrol voucher to cover the cost of travelling to and from the university. The capsules were provided at no cost to the participants.
3. Results

Current and past psychiatric diagnoses as well as previous psychiatric medications for each case are presented in Table 1 below. Demographic characteristics are presented in Table 2. The results of the intervention will first be presented as a group. In this section, results will be presented according to treatment phase; baseline, on micronutrients, withdrawal of micronutrients, reintroduction of micronutrients. Table 3 presents the scores for each case on dependent measures across each phase.
<table>
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<tr>
<th>Participant (age)</th>
<th>Current Psychiatric Diagnoses</th>
<th>Past Psychiatric Diagnoses</th>
<th>Previous Psychiatric Medications</th>
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<tbody>
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<td>Case 1 (21)</td>
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<td>Case 3 (20)</td>
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<td>Alcohol Dependence, Cannabis Dependence</td>
<td>Methylphenidate, fluoxetine, amitriptyline, lorazepam, clonazepam, clonidine, imipramine</td>
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<td>Case 4 (21)</td>
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<td>Cannabis Abuse, PTSD</td>
<td>Antidepressants, lorazepam, zopiclone</td>
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<td>Case 5 (20)</td>
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<td>Anorexia Nervosa, Restricting subtype</td>
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Table 2

Demographic Characteristics of Final Sample

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<th>Number/Mean</th>
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<tr>
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Table 3

*Changes in Outcome Measures*

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<th>Off micronutrients (A)</th>
<th>On micronutrients (B)</th>
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<td><strong>OQ Total (Self-report)</strong></td>
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DASS Total (Self-report)

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</tbody>
</table>

Note. MADRS = Montgomery Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale, GAF = Global Assessment Functioning, LIFE-RIFT = Range of Impaired Functioning Tool, OQ = Outcome Questionnaire, DASS = Depression Anxiety Stress Scales, NAS = Novaco Anger Scale, PI = Provocation Inventory. Higher scores on the GAF indicate better functioning whereas higher scores on the other measures indicate greater impairment.

a. Case 2 withdrew from the trial after four weeks off the micronutrients, did not complete self-report measures while on micronutrients

b. Case 4 was lost to follow-up following the 7.1 earthquake which coincided with the end of his first phase and a reversal was not obtained

c. Case 5 is still enrolled in the trial and therefore data collection is not complete, she is beginning the second phase of micronutrients

d. Case 1 chose to continue micronutrient treatment upon completion of the trial. She consented to a follow-up (10 months back on)
3.1 Group analysis

The primary concern of this research was mood stability, as measured by the MADRS and YMRS. A visual analysis of this data is presented in single-case, multiple-baseline format, attending particularly to the level of the problem shown, trends over time and variability within each phase. Cases are presented in the following order; from shortest baseline to longest baseline.

Baseline phase (B). Figure 1 shows that all cases had elevated depression scores, falling in the clinical range. Case 3 showed a pattern of increasing depression severity as baseline proceeded. Case 5 demonstrated a pattern of decreasing depression severity. For the other three cases, only one baseline data point was collected making it difficult to establish stability and trend.

Treatment phase (On). Figure 1 shows that the micronutrient treatment was effective at reducing depression in three of the five cases, in that their MADRS scores reduced to the non-clinical range (in remission, using a cut-off score of 10 as suggested by Hawley et al., 2002). Case 2 demonstrated a reduction in depressive symptoms although not in remission. Case 5 demonstrated a variable response in her mood symptoms during the treatment phase. She did, however, display a slight reduction in her MADRS score at 10 weeks on the micronutrients, compared to her baseline scores. Case 4 demonstrated a gradual decrease in depression severity over successive weeks of the treatment phase. Case 3 demonstrated a positive effect after the first week on micronutrients and further treatment gains were made. Case 1 demonstrated a more gradual effect over the first two weeks but then a dramatic reduction in depression severity by the third week on, rebound in symptoms (which will be discussed in her case study below) followed by a reduction again. Figure 2 shows that all five cases demonstrated a reduction in
YMRS scores, although Case 5 displayed a modest change. Cases 4 and 5 started the trial with low YMRS scores and therefore there was not much room for improvement.

_Treatment withdrawal/Reversal phase (Off)._ Figure 1 shows that depression symptoms returned to baseline severity levels in Cases 1, 2, 3 and 5. Case 4 was lost to follow-up and therefore a reversal was not obtained. Case 1’s symptoms were slower to return than for Case 3. This is consistent with the nature of their responses during the treatment phase. Case 2’s depression at two months off was actually higher than her score in the baseline phase. For Case 5, her depression symptoms returned to baseline severity after two weeks off the micronutrients. Cases 2 and 3 both displayed increased YMRS scores.

_Reintroduction of treatment (On)._ Figure 1 shows that depression again reduced (in remission) for Cases 1 and 3, replicating their responses demonstrated in the first treatment phase. Only Case 5 had some residual depressive symptoms, although she still demonstrated a reduction. YMRS again reduced to zero in Case 3.
Figure 1. Change in MADRS scores

Note: Solid lines indicates remission, dashed lines indicate different phases of trial, B = Baseline, On = On micronutrients, Off = Off micronutrients. Cases 2 and 4 dropped out prematurely.
Figure 2. Change in YMRS scores
Figure 3. Change in GAF scores
As is evident from Table 3 and Figures 1 to 3 above, two participants demonstrated clear on-off control of psychiatric symptoms, with reversal and replication of treatment benefits. Furthermore, one participant demonstrated clinically significant improvements in mood and functioning while on the micronutrients; however, he was lost to follow up following the 7.1 earthquake (which coincided with the end of his first phase on EMP+) so a reversal was not obtained. One participant demonstrated a trend toward improvements in mood while on the micronutrients and subsequent deterioration during the wash-out phase. However, she decided to withdraw from the study at four weeks off to go on psychiatric medication. Further, one participant demonstrated some improvements which will be discussed. See Table 1 for results. See Figure 1 for a graphical display of MADRS scores over time for each participant. Using a cut-off of 10 as an indicator of remission on the MADRS (Hawley, et al., 2002), three participants were in remission at post-intervention. Length of baseline varied across participants; only one data point was collected for three of the cases whereas two data points were collected for the other two cases. Longer baselines allow for stability of symptoms to be assessed and stronger inferences about the intervention causing the change in symptoms can thus be made. One case demonstrated some variability in the baseline phase with a lower MADRS score at the second baseline assessment.

Micronutrient treatment was associated with changes across a wide range of outcome measures. Data will now be presented using modified Brinley plots (Brinley, 1965). These were developed as a way of presenting data from cognitive psychology experiments (Brinley, 1965). Data is displayed as a scatter-plot, with a co-ordinate pair from each condition for each participant. If there are no systematic differences between conditions, the data points lie on or randomly about the diagonal line of no change. If there are systematic differences between conditions, the data points systematically deviate from the line; either above or below the
diagonal line. Capstick and Blampied (2004) and Blampied (2007) have argued that Brinley plots are useful in single-case research in detecting systematic effects of interventions while preserving the individual’s identity in the visual display. Time-series data are presented in which baseline scores are plotted against post-intervention scores. Systematic effects are observed as deviations from the diagonal line (line of no effect). Generally, points that fall above the line reflect deterioration and points that fall below the line reflect improvement. However, on the GAF, points above the line indicates improvement and points below the line vice versa. Arrows are displayed on the graphs, indicated desired directional change (improvement). Lines indicating cut-off scores are also displayed. Refer to Figure 4 below for an interpretation of modified Brinley plots.

*Figure 4. Modified Brinley plot interpretation (Blampied, 2011)*
See Figure 5 below for changes in clinician-rated outcome measures, displayed as modified Brinley plots. See Figures 6 and 7 for changes in self-report outcome measures and Figure 8 for changes in ADHD symptoms. Anger was reduced, as measured by the NAS-PI, in three of the four cases in which data were collected. A cut-off T-score of 65 reflects clinical elevations. Behavioural and psychiatric problems, as measured by the OQ, were reduced in two of the four cases. A score of 63 is typically used as a cut-off for identifying individuals at high risk for psychiatric problems (Lambert, et al., 2004). Depression, anxiety and stress, as measured by the DASS, reduced in three of the four cases. Cut-off scores for the DASS are as follows: 13 for Depression, 10 for Anxiety and 18 for Stress. Scores above these cut-offs fall in the moderate, severe and extremely severe ranges (Lovibond & Lovibond, 1995). In the three ADHD cases, both DSM-IV inattentive and hyperactivity/impulsivity scores reduced on the CAARS self-report and observer measures. A cut-off T-score of 65 reflects clinical elevations.
Figure 5. Brinley plots displaying change on clinician-rated measures

Note. Arrows indicate desired directional change. Graphs plotted baseline versus on, baseline versus off and baseline versus second phase on micronutrients (On 2).
Figure 6. Brinley plots displaying change in Novaco Anger Scale – Provocation Inventory (NAS-PI) and Outcome Questionnaire (OQ) scores
Figure 7. Brinley plots displaying change in DASS scores
Figure 8. Brinley plots displaying change in CAARS scores

3.2 Single Case Analysis

Each case will be described and discussed in detail below. These results will also be presented according to each treatment phase. For convenience, each participant’s data is presented in a figure associated with the section in which the individual’s results are presented.

3.2.1 Case 1: KT, a 21-year-old female

Please refer to (Rucklidge & Harrison, 2010).

Background

KT was first referred to a pediatric mental health service in 2000, at the age of 12. She was involved with a number of psychiatric services for 5 years, with a variety of presenting concerns including ADHD, hypomania, depression, Oppositional Defiant Disorder (ODD) and specific learning disabilities (maths and spelling). During this time, she was mainly treated with methylphenidate and fluoxetine, neither of which she found beneficial for extended periods of time. She took fluoxetine on two occasions, both times for a few months. Although she found fluoxetine to be beneficial in improving her mood, it made her feel “hyper” and uncontrollable and she did not like the side-effects. KT also had a history of taking methylphenidate on and off between the ages of 7 and 17, which reportedly calmed her down and lowered her impulsivity. KT reported that methylphenidate helped her concentrate at school however it made her more moody with her friends and at other times quite “flattened”. KT’s mother described her as violent, angry and almost manic when not taking methylphenidate however when KT was on her medication she was more passive, slowed down and able to reason and rationalise.

In 2003, at the age of 15, KT was assessed by a research team at the University of Canterbury using the KSADS-PL and was diagnosed with ADHD Combined Type, Oppositional Defiant Disorder, Bipolar Disorder NOS with a past history of Separation Anxiety Disorder. At
the time of the assessment she was taking methylphenidate. In 2008, KT was recruited for an 8-week open-label trial of EMP+ for adults with ADHD and mood instability. At the time she was contacted about the trial, she was not taking any medications for her psychiatric illnesses. The trial then extended into a natural ABAB design (described below). Throughout, written consent was obtained from the patient to participate in research.

**Baseline (prior to the nutritional intervention)**

Based on the K-SADS, KT met DSM-IV criteria for ADHD Combined Type, Bipolar II Disorder, Social Phobia, and Panic Disorder with Agoraphobia. Clinician-rated depression, as measured by the MADRS, was 25. See Figure 9 below. KT entered the trial in a depressed episode that had been present for two years with intermittent hypomanic symptoms. Her score on the YMRS (15) was consistent with this low mood, the score reflecting the presence of ADHD symptoms rather than heightened mood symptoms. She obtained a CGI-S of moderately ill for both depression and ADHD. KT reported significant behavioral and psychiatric concerns as reflected by her OQ score of 76. Her GAF score was 45, indicative of serious symptoms and serious impairment in functioning. The CAARS self-rating and observer measures indicated clinical elevations on measures of emotional lability, inattention and hyperactivity/impulsivity (T-scores greater than 65). KT obtained a NAS Total T-score of 68 and a Total PI T-score of 48. See Figures 10 to 13 below.
Figure 9. Time-series data displaying change in KT's MADRS scores
Figure 10. Change in KT's Outcome Questionnaire (OQ) scores

Note. SD = Symptom Distress, SR = Social Role, IR = Interpersonal Relations

Figure 11. Change in KT's Conners Adult ADHD Rating Scales (CAARS) self-report scores
Figure 12. Change in KT's Conners Adult ADHD Rating Scale (CAARS) observer-rated scores
**First intervention with EMP+**

KT began the micronutrient formula at five capsules a day, divided into three doses, and titrated up over a 1-week period to the full dose of 15 capsules a day divided into three equal doses, taken with food and plenty of water. Only minor side effects were reported, such as a mild headache and mouth ulcer but these were transient and only occurred in the first couple of weeks. KT’s compliance was excellent in that she took the full dose of 15 capsules per day (compliance assessed by number of pills dispensed and returned). KT was followed every week for an eight-week period. Although there was little change in the first two weeks (her MADRS scores stayed in the moderate range), by three weeks, there were noticeable changes in KT’s symptoms. Her mood had lifted substantially, confirmed by a MADRS score of 6 (in remission). She reported being less irritable, more motivated and more interested in life. At four weeks, KT reported feeling so much better than when she started the trial. She reported that EMP+ helped her to think more positively and she was not as scared of life anymore.

All outcome measures were repeated at eight weeks. See Figure above. Depression had reduced substantially, confirmed by a MADRS rating of 7 (in remission). This represented a 72 percent reduction from baseline. KT’s CGI-S ratings for depression and ADHD were “normal/not ill” and “minimally ill” respectively. Her CGI-I ratings for depression and ADHD were “very much improved” and “much improved” respectively. Self-report CAARS scores confirmed changes in that there was substantial improvement from baseline on measures of emotional lability, hyperactivity and impulsivity. Changes, while present, were more modest based on the observer report. Interestingly, little change was observed in the inattention subscale,
consistent with self-report. Self-reported behavioural difficulties, as measured by the OQ, reduced to a score within a range found in community samples. Her GAF score of 75 reflects a substantial improvement in overall functioning, indicative of mild symptoms. Her anger reduced, as measured by the NAS-PI, with a Total NAS T-score of 60. Her blood and urine tests were repeated and there were no changes from baseline.

After eight weeks on the formula, KT decided to come off EMP+ because she believed her improvements in mood were due to contact with the primary investigator. She thought it had been helpful talking to someone each week. Although she acknowledged the potential benefits of staying on EMP+, she decided she would stop taking the supplement and instead be more active and positive. She did not think she would remember EMP+. However, she consented to be monitored during this withdrawal phase.

_Treatment withdrawal/Reversal phase_

Two weeks after the treatment was discontinued, KT already reported being more irritable and hyperactive and at four weeks she was more “blunt, snappy and grumpy”. Two months after stopping EMP+, KT reported low mood, a lack of motivation, tearfulness and irritability. She experienced substantial difficulties in starting simple routine activities. KT reported that her co-workers noticed she was more talkative/outspoken since she had come off EMP+. Outcome measures were repeated at 8 weeks off EMP+. Her depression symptoms returned to baseline severity level, confirmed by a MADRS rating of 24. Her CGI-S ratings for depression and ADHD both returned to baseline levels (moderately ill). Most notably, self-reported and observer-reported emotional lability/impulsivity returned to baseline levels (self-reported symptoms were even higher than baseline) as well as self-reported hyperactivity/impulsivity. Her OQ score increased to 51. Overall functioning also deteriorated,
reflected by a GAF score of 60. KT concluded that she was going to end up “ruining her life” and decided to resume EMP+.

Reintroduction of EMP+

EMP+ was reintroduced and KT was seen every few months over a one-year period. Outcome measures were repeated at 8 weeks and 12 months back on EMP+. At 8 weeks back on, improvement was noted in all areas of functioning. Depression again had reduced substantially, confirmed by a MADRS score of 5 (in remission). Her CGI-S ratings for depression and ADHD were “normal/not ill” and “minimally ill” respectively. Both self-report and observer scores on the CAARS subscales of emotional lability/impulsivity, inattentive symptoms and hyperactive/impulsive symptoms showed a decrease from the previous phase of being off EMP+. Self-reported behavioural difficulties, as measured by the OQ, reduced and her overall functioning also improved, indicated by a GAF score of 75.

At 12 months back on EMP+, KT was in remission of all mental illness. Remission of depression was confirmed by a MADRS score of 0 and psychiatric interview. Her CGI-S ratings for depression and ADHD were both “normal/not ill” and CGI-I ratings were both “very much improved” since the worst phase. On the CAARS, all scores were now in the nonclinical range. Self-rated and observer-rated inattention showed reductions from baseline of 37% and 33% respectively, which represent changes of greater than 2 standard deviations (SD). Self-rated and observer-rated hyperactivity/impulsivity showed reductions from baseline of 33 percent (2 SD) and 10 percent (.5 SD) respectively. Her OQ score (22) was the lowest it had been and her overall functioning was the highest (GAF=90). Her anger reduced further, with a T-score of 40 on the NAS. Therefore, there were further improvements since the previous assessment, even without ongoing therapeutic contact.
KT did not become hypomanic at any point during this follow-up phase; her highest score on the YMRS was 15 which was at baseline. She also reported better health (sick less often and her glands were less swollen – an ongoing problem she had had since having glandular fever in high school). Although better health was not objectively confirmed, it is interesting to note. She had successfully quit smoking for 9 months.

Summary and Discussion of KT

KT is a 21 year old with BD-II, ADHD and Panic Disorder who responded to a micronutrient formula (EMP+), with improvements in all her psychiatric symptoms including anxiety, depression and ADHD. The treatment response was replicated through an ABAB design, showing on-off control of symptoms with the micronutrients. After one year she showed further gains and was in remission of all psychiatric conditions. Of notable clinical interest, no long-term side effects were reported while on EMP+. Perhaps more remarkably, KT achieved these changes after a long and well documented history of poor response to conventional treatments. However, more importantly, one intervention stabilized both ADHD and mood symptoms as well as anxiety, a finding not typically reported in the psychopharmacological literature. The changes in ADHD symptoms documented here were equivalent or larger than those reported from conventional treatments like methylphenidate (Mehri et al., 2008) or atomoxetine (Faraone et al., 2005), and are certainly larger than the placebo effects reported in these other published studies. KT’s symptoms of hyperactivity and impulsivity, at least according to self-report, changed more rapidly as compared with her symptoms of inattention, consistent with the results of the larger open label trial with adults with ADHD and mood dysregulation (Rucklidge, et al., 2011). This study found that while inattention improved after eight weeks, the means continued to fall in the clinical range whereas the improvement in the hyperactive/impulsive symptoms resulted in means that fell in the normal range (Rucklidge, et
al., 2011). However, for KT, after 12 months on the formula, her inattention symptoms had now equally improved. This self-report change was also noted by the observer report (although not to the same extent) and supported by the clinician interview. It is possible that EMP+ is having a more direct impact on the neurochemical pathways involved in inhibition, impulsivity, hyperactivity and mood regulation than inattention. However, perhaps as KT’s mood improved, she was better able to develop strategies to assist her with her inattention (Rucklidge, et al., 2011).

Interestingly, about six weeks after KT resumed EMP+ she took an antibiotic for an infection. She found her psychiatric symptoms worsened during the 10 day course of the antibiotic but again disappeared/improved once she stopped the antibiotic. Indeed, that the use of an antibiotic resulted in a re-emergence of psychiatric symptoms lends some support to the idea that nutritional deficiencies may at least in part be contributing to KT’s presentation. Although the direct effect of antibiotics on specific nutrient absorption is very difficult to assess, some research suggests that antibiotics can impair the body’s ability to absorb nutrients by changing the gut flora involved in the digestion and absorption of nutrients (Levy, 2000; Saavedra, 1999; Wynne, McCartney, Brostoff, Hudspith, & Gibson, 2004).

At five weeks on (first phase), there was a return in her psychiatric symptoms. Previous medications may have the potential to cause post withdrawal syndrome. If an individual has been on medications in the past, there will most likely be some storage of the medication in the body which eventually will be released back into the system. This can bring on post withdrawal symptoms. Drugs are stored in fat cells, muscle, bone marrow, liver, and other tender tissues in the body (Cecchini & LoPresti, 2007).

KT reported a preference of EMP+ over conventional medication in that it does not take her personality away, i.e. she can still get excited about things. KT reported that on methylphenidate, she felt she had no personality, became very withdrawn and much like a robot.
She reported that EMP+ takes away the crying, low mood and erratic behaviour/moods and stabilises her. She reported that if she could do it over again she would try EMP+ over methylphenidate.

Placebo response cannot be dismissed; however, there are several reasons that it is unlikely. First, there was no therapeutic benefit until three weeks after beginning the micronutrients. Second, KT chose to come off the treatment because she thought her symptom improvement was due to contact and care received as part of a trial. Third, the changes have been maintained for a long period of time (12 months) and placebo effects are not likely to last for this long. Indeed, her symptoms continued to show improvement over an extended period of time.

3.2.2 Case 2: JB, a 16-year-old female

Background

JB is a 16-year-old female who was based at a youth justice residential facility for the duration of the trial. She was referred to the trial by her G.P. at a youth health centre. JB had been admitted on several occasions to a pediatric mental health service, with a variety of presenting concerns including anxiety; more specifically, OCD and Social Phobia. JB also had a history of cannabis dependence, alcohol abuse and ODD. JB’s mother reported that JB had displayed severe mood dysregulation since the age of four and had been difficult to control. JB had a history of being aggressive, verbally abusive and volatile. Her mother reported that JB’s behaviour had worsened over time. JB had a history of self-harm behaviours such as forearm cutting and scratching and had overdosed twice, the first was with quetiapine and the second was with a mix of risperidone, fluoxetine and panadol. The second overdose was followed by two days of monitoring in hospital. In the past, JB has been tried on various psychiatric medications including fluoxetine, quetiapine, risperidone and moclobemide. JB reported experiencing severe
side effects associated with these medications and did not notice any improvement in her symptoms.

**Baseline (prior to nutritional intervention)**

JB has a complex psychiatric presentation. At the time of assessment, JB was based at a youth justice facility. Based on the K-SADS semi-structured clinical interview, at the age of 16, JB met diagnostic criteria for Bipolar Disorder NOS (BD-NOS), ADHD Combined Type, Social Phobia, GAD and Conduct Disorder. Her mood presentation was characteristic of severe mood dysregulation. As she was in a youth justice residential facility, she was not using alcohol and drugs at the time of assessment, although she abused them in the past. Clinician-rated depression, as measured by the MADRS, was 32 and clinician-rated mania, as measured by the YMRS, was 27. Refer to Figures 14 and 15 below. JB obtained a clinician-rated C-GAS score of 40 indicative of major impairment in functioning in several areas and unable to function in one of these areas. Further, JB obtained a LIFE-RIFT score of 17 at baseline. Self-report measures were administered at baseline. However, JB failed to complete these at eight weeks on the micronutrients and therefore it is not necessary to report on baseline self-report scores.
Figure 14. Time-series data showing change in JB’s Montgomery Asberg Depression Rating Scale (MADRS) scores

Figure 15. Time-series data showing change in JB’s Young Mania Rating Scale (YMRS) scores
First Intervention with EMP+

Only minor side-effects were noted including some headaches (four times over a two-week period), nausea and dry retch if the capsules were taken with food. However, these side-effects were transient and only occurred in the first couple of weeks. JB experienced some medical problems during the first couple of weeks, more specifically, strep throat and toothache. However, she chose not to go on antibiotics which meant she could remain in the trial. JB was followed every fortnight for an eight-week period. After two weeks on the micronutrients, both clinician-rated depression and mania, as measured by the MADRS and YMRS, were lower than baseline (scores of 25 and 13 respectively). Clinician-rated depression was reduced further (19) after four weeks and remained similar after six weeks (18). At eight weeks on, JB obtained a MADRS score of 24 and YMRS score of 22. Further, her C-GAS score reduced from 40 at baseline to 50 on the micronutrients. In addition, her LIFE-RIFT score reduced from 17 to 12, indicative of less impairment from her psychopathology. JB refused to complete the self-report measures at eight weeks on EMP+.

Treatment withdrawal

After two weeks off the micronutrients, JB’s mood remained low. She was particularly preoccupied with her appearance. After four weeks off the micronutrients, JB’s clinician-rated depression was the highest it had been over the course of the trial to date, with a score of 37 (severely ill). Furthermore, JB continued to experience significant variability in her mood. She refused to meet for the first half hour and although she finally agreed to meet, she threatened to be violent. She obtained a YMRS score of 26. JB received a C-GAS score of 40 (indicative of major impairment in functioning in several areas and unable to function in one of these areas) and an overall clinical impression of -3 (markedly worse). In terms of depression, a CGI-BP of
very much worse was obtained and in terms of mania, a CGI of much worse. At this point, JB decided to go on psychiatric medication and therefore was withdrawn from the trial.

Summary of JB

JB is a 16-year-old female with BD-NOS, ADHD, CD, GAD and Social Phobia, who demonstrated some improvements while being on EMP+, in terms of her mood stability and general functioning. However, although her mood did improve to some degree, scores on measures of mood still remained in the clinical range while on the micronutrients. Treatment gains were not replicated as she chose to go on psychiatric medication. Therefore, the ability to infer causation is limited. A further limitation was her refusal to complete the self-report questionnaires at eight weeks on the micronutrients which meant changes on other outcome measures could not be tracked. It is important to note that compliance with the treatment was excellent due to incarceration in a youth justice residential facility. In summary, the micronutrient treatment appeared to improve JB’s mood. Further, her mood deteriorated while off the micronutrients. She represented an extremely complex psychiatric case.

3.2.3 Case 3: TJ, a 20-year-old male

Background

TJ is a 20-year-old male who self-referred to the trial in February, 2010 after reading about it in the newspaper. At this time, he was not taking any medications for his psychiatric symptoms. TJ was diagnosed with ADHD at the age of two. In the past, TJ has been on various medications for his psychiatric symptoms including methylphenidate (ages 2-10), imipramine, fluoxetine, clonidine, amitriptyline, lorazepam and clonazepam. TJ reported that methylphenidate made him feel drowsy and “vegetated”.


Baseline (prior to nutritional intervention)

Based on the CAADID, TJ met DSM-IV criteria for ADHD, combined type with onset in childhood and continued symptoms to the present time. Based on the SCID-I, TJ met criteria for Major Depressive Disorder, Panic Disorder with Agoraphobia, a Specific Phobia of needles (author went with him to get blood tests done) and Substance Abuse (cannabis and alcohol). TJ entered the trial in a depressed episode, confirmed by a MADRS score of 28. His score on the YMRS (18) was consistent with this low mood, the score reflecting the presence of ADHD symptoms rather than heightened mood symptoms. CGI-S ratings were as follows: 6 for ADHD, 5 for Depression and 3 for Mania. TJ obtained a LIFE-RIFT score of 10, indicating impaired functioning due to his psychiatric symptoms. His GAF score was 51, indicative of moderate symptoms and moderate impairment in functioning.

TJ reported significant behavioural and psychiatric concerns as reflected by his OQ score of 99. In terms of scores on the DASS, anxiety (23) fell in the extremely severe range, stress (29) fell within the severe range and depression (13) fell in the moderate range. He obtained a total DASS score of 65. In terms of his ADHD symptoms, the CAARS self-report indicated clinical elevations on measures of both DSM-IV inattention and hyperactivity/impulsivity (T-scores greater than 65). Scores on this measure should be interpreted with caution as the Inconsistency Index reached 9. However, consistent scores were also obtained on the CAARS observer screen (as assessed by the author), with both DSM-IV Inattentive symptoms (T=83) and Hyperactive/Impulsive symptoms (T=79) falling in the clinical range. In terms of anger, as measured by the NAS-PI, TJ obtained a Total NAS score at the 99th percentile (T=72). The Cognitive subscale score fell at the 99th percentile (T=72), Arousal at the 96th percentile (T=68), and the Behaviour at the 96th percentile (T=67). Anger regulation was low at the 7th percentile (T=35) and his Total PI was at the 88th percentile (T=62). See Figure
A second baseline was collected a month later as there was a delay in getting the blood tests done and subsequently getting TJ started in the trial. Generally, TJ’s symptom levels were consistent over this baseline period. More specifically, his MADRS score increased slightly to 31 (see Figure 16 below) and his YMRS decreased slightly to 14. His GAF score remained the same, as well as his CGI-S ratings. His OQ increased by 4 points to 103; this increase was solely in the SR domain. TJ’s total DASS score increased to 82, with increases across all three domains, particularly depression which increased to 22 (severe range). Anxiety increased to 26 (extremely severe range) and stress increased to 34 (extremely severe). See Figures 17 to 21 below.
Figure 16. Time-series data showing change in TJ's Montgomery Asberg Depression Rating Scale (MADRS) scores

Note. B = Baseline, On = On micronutrients, Off = Off micronutrients. Solid line indicates remission. Dashed lines represent the different phases of the trial.
**Figure 17.** Change in TJ's Depression Anxiety Stress Scales (DASS) scores

*TJ’s Depression score was zero at On 2 (second phase on micronutrients)*

**Figure 18.** Change in TJ's Outcome Questionnaire (OQ) scores
Note. OQ = Outcome Questionnaire, SD = Symptom Distress, SR = Social Role, IR = Interpersonal Relations

Figure 19. Change in TJ'S Conners Adult ADHD Rating Scales (CAARS) self-report scores
Figure 20. Change in TJ's CAARS observer-rated (screening version) scores

Figure 21. Change in TJ's Novaco Anger Scale – Provocation Inventory (NAS-PI) scores

Note. NAS = Novaco Anger Scale, Cog = Cognitive, Aro = Arousal, Beh = Behavioural, Reg = Regulation, PI = Provocation Inventory
**First intervention with EMP+**

Only minor side effects were reported, such as a mild stomach ache when the pills were not taken with food and “cramps” at the back of his head, reportedly worse than headaches but these were transient and only occurred in the first couple of weeks. He also reported increased flatulence. TJ’s compliance was excellent in that he took the full dose of 15 capsules most days, only missing a few doses occasionally. TJ was followed weekly to fortnightly for a 10-week period.

Changes were noted after only a week on EMP+. TJ’s mood lifted substantially, with his MADRS score dropping from 31 to 11. TJ’s mood remained stable, with a MADRS score of 10, at two weeks on the micronutrients. However, he missed three doses over that week. TJ reported that he noticed an effect of not taking the pills on his mood. TJ reported that after two weeks on the pills, he could sit through an entire movie which he was unable to previously do and that he was now able to focus on one thing at a time. However, TJ reported that he was still experiencing difficulties in keeping track of conversations. His appetite had substantially increased since starting on EMP+ and he was now eating three meals a day and enjoying his food. At four weeks, there was a further improvement in his mood, confirmed by a MADRS rating of 5. TJ obtained a GAF score of 70, indicating an improvement in his global functioning. At six weeks on the micronutrients, TJ reported that he was able to sit still. TJ’s partner attended this appointment and reported several changes in TJ including greater motivation, being less on the go, getting to work on time, less paranoia, not as wound up and a bit more “laid back”. At eight weeks on, TJ reported that he had quit smoking the previous week and experienced cravings only every few days. He also reported a decrease in cannabis use. TJ reported an increased interest in activities, increased appetite and improved sleep.
All outcome measures were repeated at 10 weeks. TJ was no longer in a depressed episode, confirmed by a MADRS score of 0. See Figure 1. Furthermore, his YMRS score was 0. TJ’s CGI-S ratings were “minimally ill” for ADHD and “normal/not ill” for both depression and mania. CGI-I ratings were “very much improved” for both ADHD and depression and “much improved” for mania. His GAF score (80) was substantially higher than at baseline, reflecting a substantial improvement in symptom severity and functioning. TJ’s LIFE-RIFT decreased to 5, indicating no impairment in functioning. In terms of TJ’s ADHD symptoms, all of his scores on the CAARS self-report reduced substantially. Both his self-reported inattention and hyperactivity/impulsivity were no longer clinically elevated (T-scores of 46 and 41 respectively). On the CAARS observer screen, TJ’s DSM-IV Inattentive symptoms were at the 27th percentile, with a T-score of 44. Furthermore, his Hyperactive/Impulsive symptoms were at the 16th percentile, with a T-score of 40. TJ reported substantially less behavioural and psychiatric concerns as reflected by his OQ score of 21. TJ’s DASS score reduced substantially (10), with the score primarily driven by the endorsement of stress symptoms. TJ’s self-reported anger, as measured by the NAS-PI, was substantially reduced with a total NAS score at the 14th percentile (T=39). In terms of the subscale scores, Cognitive responses were at the 7th percentile (T=35), Arousal was at the 12th percentile (T=38), and Behavioural responses were at the 38th percentile (T=47). In addition, as expected based on the other scores, Regulation was rated higher than at baseline, 93rd percentile (T=65).

Treatment withdrawal/Reversal phase

After being off EMP+ for one week, a text message from TJ described feeling more stressed out and having greater difficulty with quitting smoking. At two weeks off, TJ reported smoking one pack of cigarettes over the last week and cannabis once or twice but that the
quantity smoked in these sittings was greater. TJ reported that he had not consumed any alcohol over the past week. TJ reported that he had been late to work a few times over the last week due to sleeping through his alarm and taking a while to get going. TJ reported feeling more stressed and that his body, particularly his shoulders, had been aching all day since a couple of days after stopping the pills. In terms of his ADHD symptoms, TJ reported being disorganised and forgetful. He reported difficulties in focussing at both work and home, getting distracted by everything, and quickly losing interest in things. He reported starting tasks but not finishing them. TJ reported that he was “a lot more hypo”, fidgety and could not sit still. He also reported difficulties with waiting in lines. Depressive symptoms had also returned, confirmed by a MADRS score of 22; although not as severe as baseline. In addition, he obtained a YMRS score of 11 and a GAF score of 60.

By four weeks off EMP+, TJ’s cannabis use had increased. He reported smoking cannabis every day and two packs of cigarettes over the last week (craving them more). TJ reported mood swings in that he would get agitated every couple of days and was getting annoyed at his partner and friends over small things. TJ also reported difficulties sleeping; more specifically, taking a long time to get to sleep, waking during the early hours of the morning and struggling to get back to sleep. He described feeling tired during the day. In addition, TJ reported a decrease in appetite. In terms of lassitude, TJ reported that he has to drag himself out of bed and that it is such an effort. In terms of ADHD symptoms, TJ reported that he has been forgetting “everything” and that he has to walk back to him room about four times every morning before leaving for work. He described that he has been more fidgety, restless and “terrible sitting still”. Again, he reported that he has been starting tasks but not finishing them; for example, he starts washing the dishes but doesn’t dry them. TJ reported that his partner has been saying things such as he is “more snappy, wound up and does not leave the house”. TJ reported that his mother has also noticed that he has been more stressed, wound up and on edge.
Outcome measures were repeated at 10 weeks off EMP+. Although his depressive symptoms did not return to his baseline severity level they did increase substantially, confirmed by his MADRS score of 23. See Figure 1. TJ’s YMRS score increased to 10, indicating these symptoms did not return to baseline severity; however, were heightened while off EMP+. TJ’s CGI-S ratings were “markedly ill” for ADHD, “moderately ill” for Depression and “mildly ill” for mania. TJ obtained a GAF score of 60, indicating moderate symptoms. In terms of TJ’s ADHD symptoms, both his self-reported inattention and hyperactivity/impulsivity returned to baseline severity levels, falling within the clinically elevated ranges (T-scores greater than 65). On the CAARS observer screen, although symptoms did not return to baseline severity levels, they were substantially higher than while he was on EMP+. All scores were clinically elevated, except for hyperactivity/impulsivity which fell just below the clinical cut-off, at 64. Although TJ’s OQ score (71) did not return to baseline severity level, it was substantially higher than while he was on EMP+. His LIFE-RIFT score increased to 14, indicating impairment across a range of settings due to his psychiatric symptoms. TJ’s DASS score returned to his initial baseline severity level, with a total score of 68. Both anxiety and stress fell within the extremely severe ranges, with scores of 26 and 35 respectively. Although his self-reported depression (7) did not return to baseline level, it was higher than while he was on the micronutrients. TJ’s anger scores returned to baseline severity, with a NAS Total T-score of 73 (increase of over three standard deviations from when he was on EMP+) and a PI T-score of 69 (almost a three standard deviation increase from when he was on EMP+).

While TJ was off EMP+, he described experiencing tense shoulders every day. He also reported that he could not relax unless he smoked. TJ missed appointments due to sleeping in and forgetfulness. In addition, he appeared more stressed and disorganised.
Treatment reinstatement

EMP+ was reintroduced and TJ was followed-up every few weeks over a six-month period. Appointments were either in person or over the phone. TJ again slowly titrated up to the full dose of 15 pills a day. At three weeks back on, TJ’s mood had improved, confirmed by a MADRS rating of 12 and a YMRS rating of 5. Furthermore, he obtained a GAF score of 65. TJ reported no difficulties getting to sleep. However, he described still being reasonably tense. Further improvements were noted at five weeks on, confirmed by MADRS and YMRS ratings of 2 and a GAF score of 71. TJ described that he was not on edge anymore and had no difficulties with concentration. At this time, there was a 7.1 earthquake in Christchurch and TJ’s reaction to this was monitored. He was reportedly coping well in the face of a potentially stressful situation. He obtained a total DASS score of 8 one week after the earthquake, with a depression score of zero and scores of 4 on both the anxiety and stress scales. Two weeks after the earthquake, his DASS score reduced to 5.

Outcome measures were repeated when TJ had been back on EMP+ for three months. He obtained a MADRS score of 0, confirming that he was no longer in a depressive episode. See Figure 1. He also obtained a YMRS score of 0. He obtained a GAF score of 81, indicating minimal symptoms and generally satisfied with life. TJ obtained CGI-S’s of “minimally ill” for ADHD and “normal/not ill” for both depression and mania. He obtained CGI-I’s of “very much improved” for both depression and ADHD and “much improved” for mania. In terms of TJ’s ADHD symptoms, there were no clinical elevations on either self-report or observer screening versions of the CAARS. On the CAARS – S:L, DSM-IV Inattentive symptoms fell at the 24th percentile (T=43). Furthermore, Hyperactive/Impulsive symptoms fell at the 14th percentile (T=39). On the CAARS – O:SV, DSM-IV Inattentive symptoms fell at the 58th percentile (T=52) and Hyperactive/Impulsive symptoms fell at the 27th percentile (T=44). TJ’s total OQ score (17) again reduced to a score within a range found in community samples. On the DASS, TJ obtained
a total score of 2. TJ rated himself low on all scales of the NAS-PI, consistent with the first phase of micronutrients. His total NAS was at the 5th percentile (T=34). Scores on the Cognition, Arousal and Behavioural subscales fell at the 0.5th percentile (T=24), 4th percentile (T=32) and 38th percentile (T=47) respectively. Interestingly though, his self-reported ability to regulate his anger was no higher than when he was not taking EMP+, with a score at the 12th percentile (T=38). TJ’s PI score was at the 16th percentile (T=40). TJ reported no anxiety, panic and edginess and that he had not been feeling tense. Furthermore, TJ reported that he had no difficulties concentrating. In addition, he reported that he had not been getting irritable. He also described being more active; for example, engaging in more leisure-time activities. It is interesting to note that he reported not using cannabis for about a week or two.

At four months back on, TJ’s depression remained in remission, confirmed by a MADRS rating of 1 (slight difficulty sleeping). TJ obtained a YMRS rating of 0 and a GAF rating of 81. TJ reported that he had not been experiencing tension, anxiety or panic. TJ reported that he had not smoked any cigarettes for the past four days and had not used cannabis for about six weeks. TJ failed to show to his appointment at five months on the micronutrients. He was unable to be reached on his cellphone and no contact was possible until several months later. TJ had gone away suddenly hence why we were unable to contact him. He had stopped the micronutrients for about three to four months. Several outcome measures were administered to TJ at this point to see how he was doing off EMP+. His mood had been stable. TJ reported some occasional irritability. He obtained a MADRS score of 8. TJ reported that he was feeling tense and on edge all the time and having difficulties with concentration. He reported that his mind has been wandering off more and he has been more forgetful recently. TJ described feeling more energetic and “hyper” than usual. He obtained a total DASS score of 23, endorsing anxiety and stress symptoms. In terms of TJ’s ADHD symptoms, as measured by the CAARS-O:SV, he obtained scores falling in the clinical range, more specifically he obtained T-scores of 65 and 67 on the
DSM-IV Inattentive symptoms and the DSM-IV Hyperactive/Impulsive symptoms scales respectively. His T-scores on these scales at 3 months on EMP+ were 52 and 44 (more than a two standard deviation increase).

**Summary of TJ**

TJ is a 21 year old male, with Major Depressive Disorder, ADHD, Panic Disorder with Agoraphobia, a Specific Phobia and cannabis and alcohol abuse, who responded to EMP+, with improvements in all his psychiatric symptoms including depression, ADHD and anxiety. Clinically significant changes were noted. His treatment response was replicated through an ABAB design, demonstrating on-off control of symptoms with the micronutrients. His analysis is aided by the stable baseline and the trend of deteriorating mood. It is interesting to note that his ADHD symptoms again returned after stopping EMP+ the second time. As was the case with KT, one intervention stabilised both ADHD and mood symptoms as well as anxiety, a finding not typically reported in the psychopharmacological literature. Treatment gains were maintained for a long period of time. Of interest, TJ’s nicotine and cannabis cravings and use reportedly decreased while on the micronutrients.

3.2.4 Case 4: BT, a 21-year-old male

**Background**

BT is 21-year-old male who was currently unemployed at the time of assessment and on parole. He has two children who live with his partner. BT was referred to the study in March 2010 by his General Practitioner (G.P.) at a youth health centre for a formal assessment. His G.P. wondered whether BT might be suffering from ADHD. BT sought help from his G.P. due to
issues with his partner, particularly violence towards her. BT left school without any qualifications. He went to jail in 2008 for assault and was currently on probation at the time of assessment. BT’s mother and siblings live in Australia and his father suicided when he was very young. A file review determined that BT had been hospitalised at a child and family inpatient unit in 2004 and received a diagnosis of Post Traumatic Stress Disorder and a query of Dissociative Identity Disorder. He was assessed at a local psychiatric emergency service after a phone call from his mother who was concerned that he was becoming psychotic. BT has a history of disruptive and aggressive behaviour. On one occasion he absconded from the inpatient ward, threatening nursing staff with a brick which necessitated a police call out. In the past, BT was tried on antidepressants for about six months, without any benefit. In addition, he was prescribed lorazepam for agitation and zopiclone for insomnia.

*Baseline (prior to nutritional intervention)*

Based on the CAADID, BT met DSM-IV criteria for ADHD, combined type. Based on the SCID-I, BT met criteria for Major Depressive Disorder, Social Phobia, OCD and a Specific Phobia of needles (the author went with him to get the blood tests done at the beginning of the trial as he was extremely anxious). BT reported that he uses cannabis three to four times a week; however, he stated that in the past he used it daily. He reported starting around the age of 11. BT did not disclose abuse of any other substances. Details of BT’s history of past trauma were not explored, although this information was made available through his file. Trauma included physical abuse by his stepfather, from the age of two or three years up to the age of nine. This was in the form of burning, placing in a septic tank, and physical assault.

BT entered the trial in a depressive episode, confirmed by a MADRS rating of 24. A second baseline data point revealed a MADRS score of 23, indicating a stable baseline. Refer to Figure 22 below. BT obtained a YMRS score of 12; however this is likely to reflect the presence
of ADHD symptoms rather than manic symptoms. His LIFE-RIFT score was 17, indicating a high level of impairment due to his psychopathology. BT obtained a GAF score of 41 and CGI-S scores of 6 for ADHD, 4 for depression and 1 for mania.

It took some time to get BT started on the micronutrients due to not getting his blood work done promptly. Therefore, there was a lapse of six weeks between his first baseline assessment and second (when he began the first open-label phase). The DASS and OQ were administered twice. BT’s total DASS score at the first baseline was 40, with stress and anxiety both falling in the moderate range and depression falling in the borderline normal-mild range. See Figure 23 below. His total OQ score was 68, which is above the cut-off, reflecting that BT is at high risk for psychiatric problems. Most notably, his SD score was 27 and IR was 25. SR was 16. BT’s DASS taken at the second baseline assessment was similar to the first one with a total score of 38, with depression falling in the mild range, anxiety in the borderline normal-mild range and stress again in the moderate range. BT’s total OQ score at the second baseline assessment was again consistent with the first assessment, this time slightly lower at 62. In terms of the different domains of functioning, SD and IR were both exactly the same as the first assessment (27 and 25 respectively) and SR was slightly lower, with a score of 10. See Figure 24 below.

In terms of BT’s self-reported ADHD symptoms, his score on the Impulsivity/Emotional Lability subscale of the CAARS was clinically elevated with a T-score of 68 and at the 96th percentile. In addition his DSM-IV Inattentive symptoms were clinically elevated with a T-score of 85 and at the 99.9th percentile as well as his Hyperactivity/Impulsivity symptoms which produced a T-score of 74 and were at the 99.2nd percentile. No observer version (significant other) of the CAARS was completed for BT, as he noted that no-one saw him frequently enough to track his symptoms over time. However, the observer screening version was completed by the author and DSM-IV Inattentive Symptoms fell in the clinically elevated range, with a T-score of
82 (99.9th percentile). DSM-IV Hyperactivity/Impulsivity Symptoms were also elevated with a T-score of 58 and at the 70th percentile. See Figure 25 below.

BT rated himself extremely high on the NAS-PI measuring anger. His total NAS T-score was 77 and at the 99.6th percentile. The Cognition, Arousal and Behaviour scales were all elevated with T-scores of 72 (99th percentile), 80 (99.9th percentile) and 76 (99.5th percentile) respectively. His self-reported ability to regulate his anger was low, with a T-score of 33 (4th percentile). Furthermore, BT’s PI T-score was 67 and at the 95th percentile. See Figure 26 below.

Figure 22. Time-series data showing change in BT’s MADRS scores
Figure 23. Change in BT's DASS scores

Figure 24. Changes in BT's OQ scores

Note. OQ = Outcome Questionnaire, SD = Symptom Distress, IR = Interpersonal Relations, SR = Social Relations
Figure 25. BT's CAARS self-report and observer-rated scores

Note. SR = Self-Report, Ob = Observer Screening Version
**First Intervention with EMP+**

An appointment with BT was scheduled for a week after he started on the micronutrients. However, he failed to show to this appointment and was unreachable on his cell phone. BT made contact about three weeks later. Apparently he had just got a new phone as his old one was stolen. He subsequently came in to the university that week for an appointment. At this visit BT reported that he only started taking the pills the previous week and did not report any side-effects associated with the micronutrients. BT obtained a MADRS rating of 19 and YMRS of 11. At two weeks on, BT reported missing one dose the previous day. Other than that, his compliance was excellent. There was a self-reported improvement in irritability in that he reported that he now walks away from situations in which he is annoyed and stated that he is “sick of hurting people”. At three weeks on the micronutrients, BT again reported missing one
dose the previous day but took the full dose of 15 pills on the other days. BT failed to show to
his four-week appointment. However, he was given three weeks worth of pills at the previous
appointment. At six weeks on the micronutrients, BT reported that he had been taking the full
dose except for the previous day in which he only took five pills. BT’s depression was now in
remission confirmed by a MADRS rating of 4. BT reported that he has noticed that the
micronutrients have been “slowing me down” in every way, that his mind is not going as fast and
that he is not as restless. BT described that he is able to focus and was not getting distracted. At
seven weeks on, BT reported missing all three doses the previous day. This was due to difficulty
swallowing the pills as he had a tooth ache. He also had an ear infection which he was taking
analgesics for. In terms of irritability, BT reported “letting things slide”, and that when irritated
by people or situations, he either walks away or does not say anything in order to not retaliate.

Clinician-rated outcome measures were repeated at nine weeks on the micronutrients.
BT’s MADRS score was substantially reduced from 23 at baseline to 2 (in remission) at nine
weeks on EMP+. See Figure 19. His YMRS score also reduced from 12 to 3, likely reflecting a
change in his ADHD symptoms. BT’s GAF score (60) was higher than baseline. CGI-S ratings
also improved. In terms of his ADHD symptoms, he obtained a moderately ill (4) rating.
However, in terms of depression and mania, he obtained normal/not ill ratings (1’s). His ADHD
symptoms were rated as much improved and depression as very much improved. Self-report
measures were administered at 10 weeks on EMP+. However, the results of these may be invalid
as BT had been sick for a week at the time these measures were administered and during that
time he was not consistently taking the pills. Some of his scores were higher than baseline. This
hypothesis is likely due to the observation that BT’s symptoms improved over time and he did
not report or display depressive symptoms at the nine-week assessment (MADRS 2). BT’s
ADHD symptoms also appeared to improve over time. He obtained a CAARS-Observer
(screening version) T-score of 63 (90th percentile) for DSM-IV Inattentive Symptoms. This was
a decrease of over one standard deviation from baseline. He obtained a DSM-IV Hyperactive/Impulsive Symptoms score of 56 which was similar to baseline. However, he self-reported lower Hyperactive/Impulsive Symptoms on the CAARS, with a T-score of 59 and at the 82\textsuperscript{nd} percentile. This was a decrease of one and a half standard deviations from baseline.

BT’s self-reported anger was lower than baseline although still elevated, except for PI which was within normal limits. He obtained a Total NAS T-score of 70 (98\textsuperscript{th} percentile), which was 0.7 of a standard deviation lower than baseline. Arousal was 1.5 standard deviations lower (T-score 66; 95\textsuperscript{th} percentile). Behavioural responses was almost one standard deviation lower (T = 67; 96\textsuperscript{th} percentile) and regulation was slightly higher with a T-score of 38, and at the 12\textsuperscript{th} percentile (0.5 of a standard deviation higher than baseline). Further, BT’s Total PI score was 1.5 standard deviations lower than baseline with a T-score of 52 and at the 58\textsuperscript{th} percentile.

The change in BT’s OQ score was primarily driven by an increase on the SD scale which is likely to due to being sick. Further, the change in his DASS score was primarily driven by an increase on the Depression scale. However, he had obtained a MADRS score of 2 the previous week when he was not sick.

By this time BT had been on EMP+ for about 10 weeks, he and his partner decided that EMP+ was not making any difference. It is clear that BT demonstrated clinically significant improvements in mood and functioning while on the micronutrients; however, he was lost to follow up following the 7.1 earthquake, which coincided with the end of his first phase on EMP+, and therefore a reversal was not obtained.

**Summary of BT**

BT is a 21-year-old male with MDD, ADHD, OCD, social anxiety, a specific phobia of needles, and CDD. BT responded to the micronutrient treatment with clinically significant
changes in mood. Depression was in remission by six weeks on the micronutrient formula. Clinically significant changes were also documented for other symptoms and functioning. However, BT was lost to follow up and therefore his symptoms could not be tracked following coming off EMP+, reducing the ability to infer causation.

3.2.5 Case 5: AP, a 21-year-old female

Background

AP is a 21-year old female who was referred to the trial by a psychiatrist at a local mothers and babies outpatient unit. AP has a child who was about 16-months old at the time of assessment. She is currently living alone with her son and is a full-time student at university. In 2005 AP was diagnosed with Anorexia Nervosa, Restricting subtype at the age of sixteen. She was discharged mid-way through 2006. Following a traumatic incident, AP developed symptoms of PTSD including hyper-vigilance, startle response, nightmares and avoidance behaviour such as avoiding malls and going out at night. AP suffered from postnatal depression following the birth of her son and was on various medications for her mood including quetiapine and fluoxetine and was also on medication for her sleep. AP was not administered the SCID-I, given she had already been assessed at the outpatient unit. She presented with difficulties around mood, anxiety and sleep. AP reported that she does not drink alcohol. She reported that she smokes about 20 cigarettes a day and consumes about a litre of energy drinks a day.

Baseline (prior to micronutrient supplementation)

AP entered the trial in a depressed episode, confirmed by a MADRS rating of 23. Refer to Figure 27 below. She obtained a score of 6 on the YMRS. AP obtained a score of 15 on the LIFE-RIFT, indicating functional impairment across several domains. She obtained a GAF score
of 45, indicating serious symptoms and serious impairment. In terms of self-reported depression, anxiety and stress, her total DASS score was 86. Depression (30) fell in the extremely severe range and at the 99.9th percentile. Anxiety (24) also fell in the extremely range and at the 99.9th percentile and stress (32) fell in the severe range and at the 98th percentile. See Figure 28 below. AP endorsed a wide range of difficulties on the OQ, with a total score of 103. Refer to Figure 29 below. In terms of the NAS-PI, AP self-reported a reasonably high level of anger, with a NAS Total T-score of 64 and at the 92nd percentile. Arousal fell in the clinically elevated range and at the 98th percentile (T=70). Cognition (86th percentile, T=61) and Behaviour (76th percentile, T=57) were also reasonably high but did not reach clinically elevated levels. AP’s self-reported anger regulation was low, falling at the 4th percentile (T=33). Her total PI T-score was at the 82nd percentile (T=59). See Figure 30 below. AP obtained a lower MADRS score (18) at the second baseline assessment. In order to obtain a measure of AP’s PTSD symptoms, the Child PTSD Symptoms Inventory was administered on which she obtained a score of 33, although not an ideal measure given her age.
Figure 27. Time-series data displaying change in AP's MADRS scores
Figure 28. Change in AP's DASS scores

Figure 29. Change in AP's OQ scores

Note. OQ = Outcome Questionnaire, SD = Symptom Distress, IR = Interpersonal Relations, SR = Social Role
Figure 30. Changes in AP's NAS-PI scores

Note. NAS = Novaco Anger Scale, Cog = Cognitive, Aro = Arousal, Beh = Behavioural, Reg = Regulation, PI = Provocation Inventory

First Intervention with EMP+

At one week on, AP reported that she could not swallow the pills over the weekend as she was sick and therefore missed taking about 20 pills. AP reported feeling slightly sick if pills were taken without food. No other side-effects were reported. She reported that she had not been smoking that week or drinking alcohol. AP obtained a MADRS rating of 25. At two weeks on AP again obtained a MADRS rating 25. She was subsequently followed fortnightly. At six weeks on, AP obtained a MADRS rating of 18. AP reported that her mood was probably better but that she was not sure about everything else. Interestingly, AP described that she had noticed improvements in her eyesight over the past few weeks, especially when driving at night, during lectures and completing the questionnaires. At eight weeks on, AP obtained a MADRS rating of
19, YMRS of 6 and GAF of 51. At 10 weeks on, AP obtained a MADRS score of 28. AP stated that “life is crappy”, that the last two weeks have “sucked” and that she was “pissed off at the world”. She expressed hopelessness about the future stating that the “future is only going to be a repeat of the past”. She had also experienced some panic attacks. At 11 weeks on her mood was much improved. AP obtained a MADRS score of 14, YMRS score of 4 and GAF of 51. Her self-reported anger remained similar to baseline. AP’s OQ score increased slightly from 103 to 111. However her DASS Depression score reduced from 30 to 25, anxiety from 24 to 23 and stress from 32 to 30. Her PTSD symptoms were slightly higher, with a score of 38.

Treatment Withdrawal/Reversal phase

At two weeks off the micronutrients, AP obtained a MADRS score of 10, YMRS of 7 and GAF of 55. At four weeks off, AP obtained a MADRS score of 25. She stated that her “mood is lower off the pills but concentration is better”. She also reported that she has noticed her eyesight deteriorate somewhat since coming off the micronutrients. AP’s MADRS score was 26 at both the six and eight-week appointments. At 10 weeks off, AP obtained a MADRS score of 25. Consistent with this, her DASS depression score increased from 25 on EMP+ to 31 off EMP+. Further her DASS stress score also increased from 30 to 37. Her OQ score remained the same as it was on EMP+. In terms of the NAS-PI, her NAS Total T-score dropped slightly. However, her PI T-score increased from when she was on EMP+. Her PTSD symptoms increased further to 46.

Reintroduction of EMP+

A few days after AP started back on EMP+ she got a kidney infection and was prescribed a 10-day course of antibiotics. Therefore, she stopped taking the pills and resumed EMP+ again two weeks after the completing the antibiotic course. At one week back on, AP obtained a
MADRS score of 12. She reported no anxiety or panic, just low level constant tension. At four weeks on, AP obtained a MADRS score of 15. She reported that her mood had been good over the last few weeks because lots of good things happened. AP stated that she was more relaxed and less stressed. At six weeks on, AP obtained a MADRS of 14. At eight weeks on, AP’s MADRS score reduced further to 11. She reported feeling a bit more energetic. She also stated that the pessimistic thoughts were still present but not as harsh. AP reported missing a few doses (about 20 pills). Of significant interest, AP reportedly did not experience any panic attacks over the two months she was back on the micronutrients which was a major change for her.

The 6.3 earthquake on 22nd February 2011 coincided with AP’s next appointment (10 weeks on). Contact with AP was made several days after the quake and AP was safe but her house was damaged and they had no power or water. AP had some left-over pills from when she was sick that she continued to take for a couple of weeks following the quake but had not taken any in the past week. A phone call with AP three weeks after the earthquake revealed that she had been very stressed and irritable. She obtained a MADRS score of 18. A month’s supply of EMP+ was delivered to AP’s house.

At 4 months back on, AP obtained a MADRS score of 20. AP stated that she had been eating a lot of junk food. She reported having a little more energy but that her anxiety was still bad especially due to having no power, as it was really dark and quiet. She reported that she was more jumpy than usual all the time and that she had been panicky but had not experienced any full-blown attacks over the last few weeks. She reported intense pessimistic thoughts every few days, reporting that she wanted to get out of Christchurch. At five months back on, AP was not doing well. She obtained a MADRS score of 34 and a GAF score of 41. AP reported several panic attacks over the last week, only about 30 minutes of sleep a night, no appetite (she had not eaten for about 48 hours), concentration difficulties, lassitude, anhedonia, low mood and persistent pessimistic thoughts. These difficulties are easily explained in light of the upcoming
anniversary of the traumatic event which occurred three years ago. Self-report measures were not administered at the second phase on the micronutrients, given the disruptions due to the earthquake.

**Summary and Discussion of AP**

The baseline phase should have been extended for AP to ensure stability and to establish an increasing trend; however, the intervention phase was introduced. Although AP demonstrated variability in her mood during the first phase of micronutrients, by the end of the first phase (11 weeks on), AP’s mood had improved; her MADRS score was the lowest it had been during the trial. At two weeks off the micronutrients, AP’s MADRS score had reduced further. A possible speculation is that the micronutrients were still in her system and continuing to have an effect on her mood, as her mood deteriorated substantially after this and remained consistent for the remainder of the off phase. AP’s mood subsequently improved when she went back on the micronutrients. She demonstrated a more consistent improvement the second time she went on (until near the end of the trial when her mood worsened due to the anniversary of a traumatic event). However, her mood symptoms still remained in the clinical range while on EMP+. Self-reported compliance was very good. AP was a unique case in that she presented with PTSD; her PTSD symptoms did not seem to improve on the micronutrients. It is interesting to note that AP reported improved eyesight while on the micronutrients. Mercola (2010) discussed the importance of nutrition for vision, particularly antioxidants. AP smokes regularly and oxidant stressors such as smoking can damage the eyes. In addition, the oxidant stress of the sun can damage the eyes if individuals do not have antioxidants which neutralise harmful free radicals (Mercola, 2010). EMP+ contains three antioxidants: vitamin C (ascorbic acid), vitamin E (tocopherol) and vitamin A (as retinyl palmitate). This provides a rationale for why AP may have
noticed improvements in her eyesight. However, it was not possible to collect any objective evidence to support her subjective report.
4. Discussion

4.1 Summary of Findings

This study provides some further evidence that micronutrients may be an effective treatment for some adolescents with SMD, consistent with other reports in the literature. Two participants demonstrated on-off control of psychiatric symptoms, with a reversal and replication of treatment response. Furthermore, one participant demonstrated clinically significant improvements in mood and functioning while on the micronutrients; however, he was lost to follow up so a reversal was not obtained. One participant demonstrated a trend toward improvements in mood while on the micronutrients and subsequent deterioration during the wash-out phase. However, she decided to withdraw from the study at four weeks off to go back on psychiatric medications. Further, one participant showed a variable response on the micronutrients.

The current sample reflects a group of adolescents with complex psychiatric presentations and therefore is difficult to treat. These adolescents have histories of long-standing clinical difficulties beginning in childhood. As well as SMD, participants met diagnostic criteria for one or more other psychiatric disorders including ADHD, social phobia, panic disorder, post-traumatic stress disorder, conduct, and drug/alcohol abuse. It was evident that these psychiatric symptoms significantly impaired these adolescents’ day-to-day functioning. All participants had been on psychiatric medications in the past. They either did not respond, and therefore represent treatment-resistant cases, or did not like the side-effects of psychiatric medications. Of significant clinical interest, side-effects of the current micronutrient treatment, if present at all, were only minor and transitory, confined to headaches and nausea.
As predicted, hypotheses were generally supported. In terms of the primary hypothesis that the first introduction of micronutrients would be associated with an improvement in mood, this was supported in four out of five cases. The micronutrient formula was also associated with improvements in general functioning, anger, anxiety and stress in four out of the five cases. Of the three cases that met diagnostic criteria for ADHD at study entry, all demonstrated clinically significant improvements in their ADHD symptoms at eight weeks on the micronutrients. One case (KT) no longer met diagnostic criteria for ADHD after one year. Further, two cases likely no longer met diagnostic criteria for ADHD; however, both were lost to follow-up. As hypothesised, withdrawal of the micronutrient formula was associated with deterioration in mood, general functioning, and other psychiatric symptoms, with a return to baseline, or near baseline symptom severity, in three of the four cases that were monitored over this phase. As discussed earlier, one case (BT) was lost to follow-up and therefore was not monitored while off the micronutrients. In terms of the reintroduction of the micronutrient formula, a replication of treatment response was documented in two of the three cases that were monitored during this phase. The other case (AP) did respond during this phase although did not show a clear response during the first phase of micronutrients. The hypothesis that improvements would be maintained over time was supported; specifically, improvements in the psychiatric symptoms of one participant (KT) have been maintained for almost two years now. As hypothesised, side-effects, if present were only minor and transitory. All were able to swallow the 15 pills a day except for one case who dropped out.

However, despite documented benefit for participants, compliance and acceptance of the treatment was an on-going difficulty for some, highlighting the challenges associated with treating adolescents with complex clinical presentations. Two participants dropped out early in the trial; one due to difficulties with swallowing the pills and the other due to the hassles of taking the pills. In addition, one drop-out believed the pills did not do anything for him and did
not see the point in coming in for regular appointments when there was no change. Other compliance issues included difficulty remembering to take the pills three times a day, missed doses, and not taking the capsules with food and plenty of water.

The findings of the present study are consistent with previous reports on EMP+. This study replicates findings from international studies demonstrating benefits of EMP+ in the treatment of a wide range of psychiatric conditions including BD, ADHD, OCD and Autism (Frazier et al., 2009; Gately & Kaplan, 2009; Kaplan et al., 2001; Kaplan et al., 2002; Kaplan et al., 2004; Mehl-Madrona et al., 2010; Popper, 2001; Rucklidge, 2009; Rucklidge et al., 2011; Simmons, 2002). Specifically, these benefits include a positive treatment response and minor/transitory side-effects in comparison to pharmacological treatment approaches. There is a broader literature examining the effects of micronutrients on a variety of emotional disturbances. However, different studies have used different combinations and doses of micronutrients, making it difficult to directly compare results. Nonetheless, the positive findings of the current study are also consistent with broader research documenting positive effects of multi-ingredient micronutrient formulas on symptoms of mood, stress and anxiety (Carroll, et al., 2000; Gosney, et al., 2008; Schlebusch, et al., 2000). There is a consistent pattern across studies revealing that micronutrients are associated with improvements in psychiatric symptoms and functioning.

As highlighted by Frazier and colleagues (2009), it is worthy to consider nutritional supplementation in cases that have had a long history of poor response to conventional treatment. It has been reported that many of the pharmacological treatments used for BPD, especially antiepileptic mood stabilizers, can cause metabolic disturbances in absorption and utilisation of vitamins B2, B6, D and folate (Apeland, Mansoor, Pentieva, McNulty, & Strandjord, 2003; Mintzer, Boppana, Toguri, & DeSantis, 2006). Polytherapy is common in the treatment of BPD given the multiple manifestations and complexity of the disorder (Blader & Kafantaris, 2007).
However, data supporting the use of a broad-based micronutrient supplement is promising in that it can correct multiple imbalances leading to more optimal brain functioning and therefore targeting multiple symptoms of mental illness (Kaplan, et al., 2007).

4.2 Theoretical frameworks and mechanisms of action

As discussed earlier, the rationale for examining the impact of a multi-ingredient formula is that nutrients do not function in isolation but rather, they are required in combination for optimum function. Mertz (1994) argued that single-nutrient interventions may actually result in imbalances and deficiencies in other nutrient, stating that “any substantial change of one nutrient for extended periods will affect the requirement for other nutrients with which the first interacts” (p. 1259). Single-nutrient interventions are too simple in that they do not account for the hundreds of interactions among nutrients (Mertz, 1994). The multi-ingredient approach has been gaining support in the field of physical health (see review by (Kaplan, et al., 2007)) and should also be applied to mental health.

Kaplan and colleagues discussed four conceptual frameworks of how micronutrients may improve mood (Kaplan, et al., 2007). The authors stressed that these models are not mutually exclusive and exhaustive but that they are compatible theories that may explain the pathways by which micronutrients influence mood. Firstly, it was hypothesised that unstable mood may be a manifestation of inborn errors of metabolism in key neurobiological pathways, for example, those responsible for the synthesis and uptake of neurotransmitters. Ultimately, this will have many effects on brain function as micronutrients are involved in enzymatic reactions that are responsible in the synthesis and metabolism of neurotransmitters (Kaplan, et al., 2007). Deficiencies in these micronutrients that function as essential cofactors would lead to depletions in essential neurotransmitters required for optimal functioning. Many nutrients contained in
EMP+ have been identified as deficient/low in some people with depression (e.g. vitamin B₉, vitamin B₁₂, vitamin B₆, vitamin E, calcium, iron, magnesium, zinc (Kaplan, et al., 2007)) and ADHD (e.g. zinc (Arnold et al., 2005); magnesium (Starobrat-Hermelin, 1998)). It is possible that this intervention normalised any nutritional deficiency or impaired ability to utilise nutrients that may have been contributing to psychiatric symptoms (Kaplan, et al., 2007). Kaplan and colleagues (2007) argued that individuals with genetic mutations that result in brain dysfunction, require greater quantities (higher metabolic requirement) of micronutrients to achieve normal metabolic functioning, and therefore, micronutrient supplementation with large doses of micronutrients should result in symptom improvement. A study by Suboticanec and colleagues (1990) provided some support for this theory that individuals with mental health problems may have inborn errors of metabolism or absorption. The authors found that 35 schizophrenic patients had lower levels of fasting plasma vitamin C as well as lower urinary vitamin C excretion in an ascorbic acid load test, compared to 35 normal controls. The group difference in plasma levels, but not in urinary excretion, disappeared with supplementation with 1 gram of vitamin C. The authors argued that the patients with schizophrenia appeared to have a higher metabolic requirement for vitamin C (Subotianec, et al., 1990).

Secondly, Kaplan and colleagues (2007) proposed that unstable mood may be a manifestation of deficiencies in the methylation of molecules. There are hundreds of methylation reactions (adding a methyl group, CH₃, to a molecule) in human brains, switching on genes, activating enzymes and regulating protein. Neurotransmitter synthesis requires methylation. S-adenosyl-L-methionine (SAMe) is a “methyl donor”, transferring a methyl group (CH₃) in the synthesis of many neurotransmitters. “SAMe is also involved in many methylation reactions in the central nervous system, including the methylation of proteins, nucleic acids, phospholipids, and neurotransmitters” (Bottiglieri, 1996 cited in Kaplan, 2007, p. 755). Folate and cobalamin are involved in the methylation of homocysteine to methionine and in the synthesis of SAMe.
Animal research has found that vitamin B12 or folate deficiencies result in an inadequate supply of methionine synthase which subsequently disrupts the methylation process (Scott, Molloy, Kennedy, Kennedy, & Weir, 1994). Bottiglieri and colleagues (2000) found that methylation was deficient in 24 depressed patients. Research has shown that SAMe results in significant improvement in mood symptoms (see review by Kaplan, et al., 2007). Kaplan and colleagues (2007) also argued the importance of being open to bidirectional causality in that deficient methylation reactions may result in depression; however, it may be the case that depression impairs methylation.

Thirdly, it was proposed that nutritional deficiencies may alter gene expression and subsequently lead to mood instability. It is now well-established that nutrients can alter gene expression (see Kaplan et al., 2007).

A fourth framework proposed by Kaplan and colleagues (2007) was that mood instability may be the result of long-latency effects of nutrient deficiencies. Many individuals do not experience their first episode of mental illness until they reach adulthood suggesting the role of long-latency deficiencies. It may also be the case that psychiatric disorders reflect progressive brain changes (Kaplan, et al., 2007).

Biological mechanisms of action have also been proposed in order to explain the positive effects of B vitamins on ADHD symptoms. Dopamine agonists such as methylphenidate are effective in the treatment of ADHD, through inhibiting dopamine transporter action (DAT). Shaw and colleagues proposed a common neuro-chemical mechanism of action between B vitamins and methylphenidate, as they both have similar molecular structures (Shaw, Rucklidge, & Hughes, 2010). Because of these important molecular similarities, “vitamin B1 might occupy the DAT binding site, so reducing the efficiency of dopamine transport from the synapse and consequently, have pharmacological properties similar to methylphenidate, which acts by the same mechanism” (Shaw et al., 2010, p 4).
There is also an emerging literature investigating the role that mitochondria play in psychiatric disorders. Recent studies suggest that the manufacture of adenosine triphosphate (ATP), the energy source of the mitochondria, is compromised in bipolar disorder and ADHD, as well as other mental illnesses (Gardner & Boles, 2005; Russell et al., 2006; L. T. Young, 2007). Although still in its infancy, there is a growing body of literature suggesting that micronutrients can be used to treat mitochondrial diseases (Parikh et al., 2009). Therefore, a possible mechanism of action of EMP+ is by increasing mitochondrial energy metabolism. Some individuals have a higher genetic need for nutrients and increasing nutrient levels can partially restore enzyme activity (Ames, Elson-Schwab, & Silver, 2002). Those with a higher genetic need for nutrients may require more than the recommended daily allowance.

Depletion of nutrients in the food supply could also be considered. Studies have indicated that the mineral and trace elements of fruit and vegetables have been decreasing dramatically over the past 50 years (Ekholm et al., 2007; Mayer, 1997). New Zealand has depleted levels of important trace minerals such as selenium (Thomson & Robinson, 1980). It may be that some individuals are especially vulnerable to these nutritional depletions in food due to different biochemical needs (Rucklidge, et al., 2011).

### 4.3 Limitations

A limitation of the study was the open-label nature of the design, in which participants knew what they were taking and their response may have been influenced by expectancy effects. Although a placebo response cannot be ruled out, there are several compelling reasons why it is unlikely to explain the therapeutic effects; for example, there was no therapeutic benefit until several weeks after beginning EMP+ in some cases and changes were maintained over a long period of time (a year in one case). However, this was a pilot study investigating whether
micronutrients may improve mood in a group of adolescents with SMD. The promising results highlight the need for future placebo-controlled research with this population.

It is also possible that other factors may contribute to explaining some of the positive effects; for example, better daily routine of getting out of bed, drinking plenty of water (improved cognition), exercise (Stathopoulou, Powers, Berry, Smits, & Otto, 2006), and a healthier diet (Rogers, 2001). Factors such as exercise and healthy diets are known to influence mood and may have contributed to the documented positive effects.

Participation in research trials involves provision of quality care, weekly contact, therapeutic input and assistance provided to ensure treatment compliance. The therapist effect may be a possible explanation for the documented improvements. However, individual contact with the investigators is unlikely to explain the dramatic changes in symptoms as this contact was gradually tapered off over time and contact over the last nine months in case one, when the symptoms were in remission, was negligible. Contact with the investigators occurred even when participants were not taking the micronutrients, indicating that contact alone cannot explain presence or absence of symptoms. Changes were maintained and even further improved after the trial in one case, highlighting that therapist contact was not the only factor involved. Furthermore, appointments were short and minimal with a focus on reviewing symptoms only rather than strategies to deal with them. Experimenter bias may have played a role, however, multi-informant measures were employed to track symptoms over time. Again, this highlights the need for double-blind, randomised controlled trials.

Spontaneous remission of symptoms is a potential explanation for improvement. However, earlier data in one case highlighted that her psychiatric symptoms were present for a long time. Second baselines, approximately a month after the first baseline, were also collected for two cases. These generally revealed no change in symptom levels. Therefore, spontaneous remission of symptoms is an unlikely hypothesis to explain the documented improvements in
psychiatric symptoms. It is possible that participants changed their diets as a consequence of their involvement in this trial; however, as diet was not adequately assessed, we cannot determine the extent that such changes may have influenced the outcome.

This study examined the impact of micronutrients on mood symptoms in only a small number of participants, and therefore generalisability of these findings is limited. Further, these case studies represent a heterogeneous group of adolescents with complex psychiatric presentations and therefore, results should not be generalised to the entire population of adolescents with SMD. Presence of a co-occurring psychiatric disorder was not excluded in this study and therefore the participants are not a pure SMD group. However, this sample may be more representative of typical clinical populations where co-occurring symptoms and disorders are the rule not the exception. Therefore, these findings may be more easily translated into clinical practice. The majority of research does not include a number of different conditions within the same study to examine the effect of a treatment. The fact that we chose a complex group of adolescents with a number of presenting problems has clinical relevance in that these types of individuals are encountered in clinical practice. In the current study, as with previous research on EMP+, improvements were documented across a wide range of symptoms including anxiety, stress levels, depression, anger control, quality of life and ADHD symptoms.

4.4 Feasibility

As with any treatment approach, feasibility is an important issue to consider. There were significant issues with recruitment of this population for an unconventional treatment study. Recruitment was initially restricted to the local health board; however, a lack of referrals through this avenue meant recruitment was extended to other services. The specific population was also broadened from BD to SMD. The age range was also extended from 16-19 to 16-21 years of age. Recruitment was initially very slow; however, picked up in the second year of the study.
Another important issue to consider in terms of feasibility is compliance with the treatment regimen. Problems with compliance included difficulty with swallowing the pills, a reason for one participant dropping out. Other challenges for the individual included the large number of pills they were required to take each day, the size of the pills, remembering to take the pills, and the after-taste. Further, the cost of continuing micronutrient treatment is another important factor to consider in terms of feasibility of this treatment approach. Challenges for the researchers included contacting the adolescents (no landlines, no money on their cell phones and therefore unable to listen to voice mail messages or reply to text messages etc.), getting them to the university for appointments (i.e. sleeping in, forgetting). Text reminders which were offered to the participants appeared to be beneficial to remembering to take the pills three times a day with meals.

Feasibility issues in terms of this kind of research included the heavy involvement required of the participants (i.e. regular appointments, wide range of measures: questionnaires, blood tests). As some of the participants in this study were from low SES groups, ongoing health problems were common, for example ear infections and tooth aches were a major concern for one participant, and others were regularly sick. A difficulty of working with this age group was the many missed appointments due to sleeping in, forgetting or being disorganised; for example, double-booking and a poor sense of time, which is a feature of ADHD. Ongoing crises were a feature of these adolescents’ lives which made working with this group particularly difficult.

### 4.5 Conclusion

In conclusion, the results of the current study provide further support that micronutrient treatment is associated with improvements in psychiatric symptoms and functioning. Further research, such as randomised clinical trials and studies investigating the mechanisms of action, appear warranted. The effects of a multi-ingredient micronutrient formula on psychiatric
symptoms with a range of age group, including children and elderly, and different psychiatric populations should be explored (i.e. schizophrenia, drug dependence). Further, results need to be replicated which will strengthen the evidence base. If a single intervention is found to be effective for a wide range of psychiatric symptoms, it would be ground-breaking in the field of mental health. It is important that researchers and clinicians are willing and open to explore this possibility.
5. References


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