Effect of Micronutrients on Behavior and Mood in Adults With ADHD: Evidence From an 8-Week Open Label Trial With Natural Extension

Julia Rucklidge, Mairin Taylor and Kathryn Whitehead

Journal of Attention Disorders 2011 15: 79 originally published online 13 January 2010
DOI: 10.1177/1087054709356173

Journal of Attention Disorders
15(1) 79–91

DOI: 10.1177/1087054709356173
http://jad.sagepub.com
SAGE

Effect of Micronutrients on Behavior and Mood in Adults With ADHD: Evidence From an 8-Week Open Label Trial With Natural Extension

Julia Rucklidge,[1] Mairin Taylor,[1] and Kathryn Whitehead[2]

Abstract

Objective: To investigate the effect of a 36-ingredient micronutrient formula consisting mainly of minerals and vitamins in the treatment of adults with both ADHD and severe mood dysregulation (SMD). **Method**: 14 medication-free adults (9 men, 5 women; 18-55 years) with ADHD and SMD completed an 8-week open-label trial. **Results:** A minority reported transitory mild side effects. Significant improvements were noted across informants (self, observer, clinician) on measures of inattention and hyperactivity/impulsivity, mood, quality of life, anxiety, and stress all with medium to very large effect sizes (all *p*s < .01); however, the mean of inattention remained in a clinical range whereas the means on measures of mood and hyperactivity/impulsivity were normalized. Follow-up data showed maintenance of changes or further improvement for those who stayed on the micronutrients. **Conclusions:** Although this study, as an open trial, does not in itself prove efficacy, it provides preliminary evidence supporting the need for a randomized clinical trial of micronutrients as treatment for the more complex presentations of ADHD.

Keywords

ADHD, treatment, minerals, vitamins, micronutrients, severe mood dysregulation

ADHD is one of the most common childhood disorders, characterized by problems with inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2000) with worldwide-pooled prevalence estimates for childhood ADHD falling at 5.29% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). It is now estimated that as many as 4% to 5% of adults may suffer from ADHD (Almeida Montes, Hernandez Garca, & Ricardo-Garcell, 2007; Kessler et al., 2006). Response to medications tend to be lower in adults with ADHD as compared to children with ADHD; it is estimated that between 34% and 78% of adults with ADHD will respond to psychopharmacological interventions with placebo responses rates ranging from 11% to 56% (Torgersen, Bjervan, & Rasmussen, 2008). Methylphenidate shows the best response rates (66%-76%) in adults with ADHD with no co-occurring conditions (Biederman et al., 2006; Spencer et al., 2005). For the few studies that have included participants with other psychiatric conditions, the response rates are below 40% (Torgersen et al., 2008). However, as 75% of adults with ADHD have at least one additional diagnosis, the relevance of the medication trials to clinical practice is questionable (Kolar et al., 2008; Torgersen et al., 2008). Furthermore, long-term effectiveness is rarely evaluated. Indeed, in the two follow-up studies found (up to 12 months), almost none of the participants were still taking the medication (Gualtieri, Ondrusek, & Finley, 1985; Mattes, Boswell, & Oliver, 1984).

Given that at least a fifth of the adult ADHD population (higher if other problems are present) do not respond to pharmaceutical medications or have adverse effects like nausea, cardiovascular side effects, insomnia, and agitation, many individuals seek other treatments for ADHD symptoms (Baumgaertel, 1999). Reviews on alternative treatments for ADHD (Arnold, 1999; Rucklidge, Johnstone, & Kaplan, 2009) indicate that the number of peer reviewed studies on such treatments is very limited in comparison to the hundreds on psychopharmacological approaches. Studies investigating one ingredient at a time have shown some promise (e.g., zinc/zinc sulphate; Akhondzadeh, Mohammadi, & Khademi, 2004;

[1]University of Canterbury, Christchurch
[2]Mothers and Babies Inpatient Unit, Canterbury District Health Board

Corresponding Author:
Julia Rucklidge, Department of Psychology, University of Canterbury, Private Bag 4800, Christchurch, New Zealand
Email: julia.rucklidge@canterbury.ac.nz

Bilici et al., 2004); magnesium; Starobrat-Hermelin & Kozielec, 1997), other nutrients show mixed responses across studies (e.g., acetyl-l-carnitine; Arnold et al., 2007; Van Oudheusden & Scholte, 2002) and other individual nutrients simply have no support for their use in the treatment of ADHD (e.g., phenylalanine; Wood, Reimherr, & Wender, 1985; L-tyrosine; Nemzer, Arnold, Votolato, & McConnell, 1986; Reimherr, Wender, Wood, & Ward, 1987). However, this approach of using one ingredient at a time may be too simplistic, as interventions of single ingredients may actually upset nutritional balances, creating deficiencies in other nutrients (Mertz, 1994). Individual nutrients work in combination with each other as well as act as cofactors in enzymatic reactions (Kaplan, Crawford, Field, & Simpson, 2007). Therefore, a more effective nutrient intervention to evaluate for mental or physical health may be one containing a broad array of balanced nutrients.

There have been several case reports showing off-on-off-on control of mood lability, aggression, and Obsessive Compulsive Disorder symptoms using a multinutrient formula, distributed under the name of EMPowerplus[1] (EMP+; Frazier, Fristad, & Arnold, 2009; Kaplan, Crawford, Gardner, & Farrelly, 2002; Rucklidge, 2009). Open-label trials have also shown positive and significant symptom reductions. Results from a 6 month study of 11 patients indicated a 55% to 66% reduction in symptoms reported on a measure of depression and an overall psychiatric measure and a 50% decrease in the need for psychiatric medications (Kaplan et al., 2001). Twenty-two private practice patients were monitored and 19 (86%) were reported to benefit from the supplement (Popper, 2001). Similarly, of 19 patients monitored clinically by a different psychiatrist, 16 (84%) improved on the supplement; in 12 (63%) the improvement was "marked" (Simmons, 2003). Kaplan, Fisher, Crawford, Field, and Kolb (2004) completed a case series to further test the impact of EMP+ in 11 children aged 8-15 with mood and/or behavioral problems (6 had ADHD). For the 9 completers, improvement was significant on most outcome measures. A large database analysis of 682 adults with bipolar disorder taking EMP+, found that 53% experienced 50% improvement in psychiatric symptoms at 6 months (Gately & Kaplan, 2009).

This research on multi-ingredient approaches to the treatment of mood instability could be of relevance to ADHD given that many now conceptualize ADHD not as a disorder of attention per se but a disorder of self-regulation (Nigg, 2001). Indeed many researchers include poor affect regulation as a core feature of the disorder (Barkley, 1997; Skirrow, McLoughlin, Kuntsi, & Asherson, 2009). Furthermore, given that up to 70% of adults with ADHD may have a history of a mood disorder (Rucklidge & Kaplan, 1997), it is essential that treatment studies consider the full picture of problems associated with ADHD rather than just the core diagnostic features. As such, a treatment that has shown promise for individuals with mood instability may also have a positive impact on those with problems with self-regulation, including ADHD.

Method

All study procedures were approved by both the University and Health and Disability Ethics Committees. All participants signed consent forms after being told about the experimental nature of the treatment. They were also informed of other treatments available in the community.

Participants were recruited through on-going university research files or from new referrals from the public service, private clinicians, and self-referrals. They had to meet criteria for ADHD based on the Conners' Adult ADHD Diagnostic Interview for *DSM-IV* (CAADID; Epstein, Johnson, & Conners, 2002), a semistructured interview whereby both current symptoms and past symptoms of ADHD are assessed as well as a thorough developmental history. In those cases where the participant no longer recalled childhood, significant others, preferably a parent or sibling, were contacted. In some cases, confirmation was obtained from school report cards or previous psychiatric assessments. In addition, participants had to have at least one elevation (> *T*-score 65) on one of the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) (*DSM-IV*) subscales of the Conners' Adult ADHD Rating Scales (CAARS; Conners, Erhardt, & Sparrow, 2003) on *either* the self or the observer versions. The Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version (SCID-I; First, Spitzer, Gibbon, & Williams, 2002) was administered to assess for co-occurring disorders as well as to determine if another mental disorder could better account for the ADHD symptoms.

The SCID-I was also used to determine presence of severe mood dysregulation (SMD) (endorsement of chronic or episodic symptoms of irritable, low or elevated mood either currently or in the past although not necessarily meeting full criteria for a mood disorder). SMD is a term used in the pediatric literature to identify children showing chronic mood lability as opposed to something episodic, more classically observed in Bipolar Disorder (Baroni, Lunsford, Luckenbaugh, Towbin, & Leibenluft, 2009) and captures mood instability more commonly associated with ADHD. Participants also required a clinical global impression (CGI) score of at least 4, indicating moderate impairment. All clinical interviews were conducted by clinical psychologists or senior graduate students. All cases were discussed with a senior clinician (JR).

Each participant assessed as having ADHD and SMD was invited to participate in the initial screening for the study. Only individuals off psychiatric medications were considered (that is, medication–free for at least 4 weeks).

Participants were not encouraged to come off a conventional treatment in order to participate in this trial. Out of a database (collected from 2001-2008) of 83 individuals with ADHD, 32 had both ADHD and evidence of SMD; 17 of those were contacted by phone (the remaining had moved and could not be found or did not return calls), seven of the 17 were not eligible as they were now taking medications to treat psychiatric problems, and two declined to participate, leaving eight. The other seven of the initial 15 participants were newly referred by the same referral sources as the other participants. One participant had to discontinue the trial after 3 days as she developed a urinary tract infection (she had an extensive history of them) and required antibiotic treatment, an exclusion criteria for the study (see below) due to the impact that antibiotics may have on gut health and nutrient absorption (Wynne, McCartney, Brostoff, Hudspith, & Gibson, 2004).

All of the other 14 participants (9 males, 5 females) completed the 8-week open label trial with EMP+. Mean age was 37.53 (*SD* = 9.56). Six (43%) met criteria for ADHD Predominantly Inattentive Type and eight (57%) met criteria for ADHD, Combined Type. Other current diagnoses included: 10 had a major mood disorder (7 major depressive disorders (MDD; 50%) and 3 Bipolar Disorder II (BDII; 21.4%)), 6 Social Phobia (42.9%), 3 generalized anxiety disorder (GAD; 21.4%), and 3 drug/alcohol abuse (21.4%). See Table 1 for a description of each participant in the trial including past history of medications.

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. Four of the six referred by a psychologist chose to discontinue their therapy during the trial and the other two met with a marital therapist a total of two sessions each throughout the trial.

Prior to inclusion in the study, 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). A copy of the results was provided to the participant's general practitioner (with consent). Furthermore, all lab results were reviewed by our study psychiatrist. This blood screening was repeated post 8 weeks of intervention and urine pregnancy tests for females were also performed monthly throughout the trial. Participants were also asked to monitor any side effects or unusual events that may have happened during each week.

Intervention

The baseline assessment was followed by an open-label acute trial with EMP+ for an 8-week period. During this time, participant progress was monitored weekly or fortnightly using outcome measures at specified intervals. Capsules were dispensed at these assessment times and participants were asked to monitor compliance with a diary. In an attempt to make the dosing simple for participants to follow, the instructions to the participants were to take 5 capsules a day initially, divided into three doses (2, 2, 1) and increase to 10 capsules a day after 3 days, divided into three doses (4, 3, 3). At the 7th day, they increased to the full dose of 15 capsules per day, preferably in 3 doses of 5 capsules and always taken with food and plenty of water. Safety, compliance, and adverse effects were assessed at each visit.

Measures

All cases were monitored by the primary investigator (JR) and a consultant psychiatrist (KS). Severity of symptoms of depression, mania and ADHD were assessed weekly or fortnightly by the clinician using: (a) The clinical global impressions severity (CGI-S) and clinical global impressions improvement (CGI-I) Scales (CGI; 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*); (b) The global assessment of functioning (GAF; American Psychiatric Association, 2000), a numeric scale (1 through 100) used by mental health clinicians and doctors to rate the general functioning of adults; (c) The Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978), an 11 item scale administered by a trained clinician who assigns a severity rating for each item based on a personal interview; and (d) The Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), a 10 item scale administered by a trained clinician

Table 1. Participant Characteristics

Participant	Past Medications	Past Diagnoses	Current Disorder	MADRS (Clinician)			CAARS SELF DSM Inattentive (*T*-Scores)			CAARS SELF DSM Hyperactivity/Impulsivity (*T*-Scores)		
				Baseline	Post 8 Weeks	Follow Up	Baseline	Post 8 Weeks	Follow Up	Baseline	Post 8 Weeks	Follow Up
1[a]	none		ADHD combined, GAD, MDD	28	11	4	90	90	74	85	66	51
2[a]	Fluoxetine, citalopram, moclobemide, valium, clonazapam, respiridone, alprazolam	MDD, drug and alcohol dependency	ADHD inattentive, MDD, social phobia	23	8	11	85	62	59	49	39	39
3[b]	none	MDD	ADHD inattentive	7	4	9	72	63	63	57	48	52
4[b]	none	Alcohol and drug dependency	ADHD combined, MDD, alcohol abuse	26	4	9	84	80	87	86	81	78
5[b]	Methylphenidate, fluoxetine		ADHD combined, BD II, social phobia, panic disorder with agoraphobia,	25	7	24	65	63	60	64	50	61
6[b]	St John's Wort, methylphenidate	MDD	ADHD inattentive, GAD	9	6	4	72	56	77	59	41	46
7[b]	Sodium valproate, citalopram		ADHD inattentive, BD II, social phobia, psychotic disorder NOS	33	3	11	90	83	64	51	43	38
8[b]	Methylphenidate, clonidine, venlafaxine		ADHD combined, BD II, social phobia	21	9	20	82	90	90	71	71	79
9[a]	none	Drug and alcohol abuse, panic disorder with agoraphobia	ADHD inattentive, OCD, PTSD, MDD	24	7	10	85	68	85	67	55	57
10[a]	Citalopram, Methylphenidate, Paroxetine	MDD	ADHD combined, Social phobia	20	11	14	90	79	72	76	71	74
11[c]	Fluoxetine	Panic disorder with agoraphobia, GAD	ADHD inattentive, MDD, social phobia	24	13		78	74		70	52	
12[a]	none	Drug & alcohol dependency	ADHD combined, drug abuse	15	2	0	74	44	44	67	52	45
13[a]	Fluoxetine	MDD	ADHD combined, GAD, OCD, MDD	32	5	6	90	62	59	69	52	45
14[a]	none	PTSD	ADHD combined, MDD, GAD	28	11	4	67	60	58	70	64	59

Note: MDD = major depressive disorder; GAD = generalized anxiety disorder; PTSD = post-traumatic stress disorder; ADHD = attention-deficit/hyperactivity disorder; OCD = obsessive compulsive disorder; BD = bipolar disorder; MADRS = Montgomery Asberg Depression Rating Scale; CAARS = Conners Adult ADHD Rating Scale.

a. Participant was on EMP at least 8 weeks at follow-up.

b. Participant was off EMP at least 8 weeks at follow-up.

c. Declined to complete follow-up assessment.

who assigns a severity rating for each item of depression based on a personal interview. An independent second rater (a psychiatrist) attended six (42.6%) of the follow-up assessments and independently scored the MADRS. Inter-rater reliability (intra-class correlation) was estimated at .956.

In addition to the above measures, at baseline and post 8-weeks, the clinician also completed the range of impaired functioning tool (LIFE-RIFT; Leon et al., 2000), which explores psychosocial functioning over the previous week in four domains: work, interpersonal relations, recreation, and global satisfaction.

Self-report measures were also used to assess mental symptoms: (a) The CAARS (Conners et al., 2003), which includes subscales assessing inattention and memory problems, hyperactivity and restlessness, impulsivity and emotional lability and problems with self-concept. It also has three *DSM-IV* subscales for inattention, hyperactivity/impulsivity and combined inattention and hyperactivity/ impulsivity. 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 was completed by an observer familiar with the adults' behaviors; (b) The Outcome Questionnaire (OQ; Umphress, Lambert, Smart, Barlow, & Clouse, 1997), a 64-item measure of treatment progress for adults receiving mental health intervention, involving three subscales: intrapersonal distress; interpersonal relations; and social problems. 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; (c) The Depression and Anxiety Stress Scales (DASS; Lovibond & Lovibond, 1995), a 42-item questionnaire which assesses an individual's self-perception of levels of symptoms relating to depression, anxiety, and stress. The manual provides cut off scores for normal, mild, moderate, and severe depression; and (d) The Novaco Anger Scale (NAS-PI; Novaco, 2003) was used as a comprehensive measure of anger. This 60-item scale consists of four domain scores (Cognitive, Arousal, Behavioral, and Regulation). Our five primary outcome measures selected a priori were the CGI, MADRS, the YMRS, and the CAARS self and observer DSM subscales and emotional lability. All tests were two tailed and any *p* values less than .01 were considered statistically significant. The effect size for each outcome variable was calculated by dividing the absolute value of the mean of the paired difference by the standard deviation of the difference.

Results

ADHD and Mood Instability

Paired sample *t*-tests revealed significant improvements on all five outcome measures assessing mood (depression (MADRS), mania (YMRS) and emotional lability (CAARS)), as well as ADHD symptoms (inattention and hyperactivity/impulsivity), both according to self and observer reports (Table 2). Effect sizes (Cohen's *d*) confirmed that the changes were large and clinically meaningful. Although the YMRS was administered, none of the participants were in a manic or hypomanic phase throughout the trial.

Using 30% as a measure of a clinically significant symptom reduction in *raw* ADHD symptoms on the CAARS, a decrease typically used to classify responders (Medori et al., 2008), 4 of the 14 participants (28.7%) would be classified as significantly improved on inattentive symptoms and 10 of 14 (71.4%) would be classified as significantly improved on hyperactive/impulsive symptoms. The mean self-report scores changed by about a standard deviation and about a half a standard deviation based on observer reports.

On the MADRS, where 50% is typically used as a measure of significant change, 10 (83.3%) of the 12 participants whose baseline scores were >9 showed a clinically significant improvement. These data are consistent with the overall clinical impression (CGI) whereby 12 (85.7%) of the 14 participants were rated as either moderately or markedly improved post 8-weeks. The CGI-I depression and ADHD scores were consistent with the changes noted on the CAARS and MADRS respectively, in that 7 (50%) were rated as very much or much improved on ADHD symptoms, and 10 (83.3%) of the 12 who entered the trial with clinically elevated symptoms of depression were rated as much or very much improved in their mood symptoms. Alternatively, using a cut off of <10 as an indicator of remission on the MADRS (Hawley, Gale, & Sivakumaran, 2002), of the 12 participants who entered the trial with clinically elevated symptoms of depression, 8 (66.7%) were in remission post 8-weeks. Figure 1 shows the scores on the weekly MADRS, using the last observation carried forward if a participant missed an appointment or was not seen that week. The mean number of sessions was 6.29 (*SD* = .99). These changes in depression on clinician ratings were consistent with pre-post self-report measures of depression, anxiety, and stress (see Table 2) using the DASS.

Quality of Life and Overall Symptom Distress

Quality of life on the Life-Rift improved (a decrease in score indicates better quality of life across employment, relationships, and recreation) and overall levels of distress, as measured by the OQ, decreased over the 8-week period (Table 2). The changes are large and clinically meaningful—the mean on the OQ at post 8 weeks was within the range of a normal community sample.

Anger and Aggression

According to self-report on the NAS-PI, there was a significant drop in self-reports of arousal and behavioral responses

Table 2. Baseline and Post 8-Week Data on Primary and Secondary Outcome Measures

	Baseline		8-Weeks Post				
Variable	*M*	*SD*	*M*	*SD*	Paired *t*-Test	*p*	Effect Size[a]
MADRS total	22.50	7.70	7.21	3.42	7.33	<.001	1.96
YMRS	2.71	3.67	0.71	1.64	3.06	<.01	0.82
Self-report CAARS (*T*-scores)							
Emotional lability	67.79	11.01	59.93	11.53	4.85	<.001	1.29
DSM inattention	80.29	8.90	69.57	13.49	3.67	<.001	0.98
DSM H/I	67.21	10.94	56.07	12.62	7.04	<.001	1.88
DSM combined	77.79	8.35	65.14	13.06	5.92	<.001	1.58
Observer CAARS (*T*-scores)							
Emotional lability	67.07	11.02	55.79	12.50	5.44	<.001	1.45
DSM inattention	70.79	8.45	64.71	10.04	2.48	<.01	0.66
DSM H/I	64.79	10.00	57.43	12.38	2.62	<.01	0.7
DSM combined	70.43	8.09	63.21	10.93	2.63	<.01	0.7
GAF	53.71	6.26	69.86	6.53	–9.14	<.001	2.44
CGI-S ADHD	4.93	0.47	3.14	0.86	9.55	<.001	2.55
CGI-S Depression	4.14	1.29	1.86	1.17	6.75	<.001	1.80
Life rift total	13.93	3.25	10.57	1.87	5.44	<.001	1.45
OQ total	80.00	19.87	57.79	21.41	3.84	.001	1.02
DASS depression	16.93	9.26	7.14	6.10	4.06	<.001	1.08
DASS anxiety	11.57	9.35	3.64	2.59	3.30	<.01	0.88
DASS stress	19.43	9.97	10.07	7.30	4.78	<.001	1.27
DASS total	47.93	24.91	20.79	13.92	4.49	<.001	1.2
NAS total *T*	56.79	8.16	49.86	8.42	3.40	<.01	0.91
NAS cognition *T*	55.79	9.55	50.64	10.72	2.62	<.01	0.70
NAS arousal *T*	60.07	9.80	51.43	7.04	3.53	<.01	0.94
NAS behavior *T*	53.21	8.60	49.14	7.46	3.10	<.01	0.83
NAS regulation *T*	44.14	9.98	50.36	9.11	–4.01	<.001	1.07

Note: MADRS = Montgomery-Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; CAARS = Conners' Adult ADHD Rating Scale; H/I = hyperactivity/impulsivity; GAF = global assessment of functioning; CGI-S = clinical global impression severity; OQ = Outcome Questionnaire; DASS = Depression, Anxiety, and Stress Scale; NAS = Novaco Anger Scale.
a. Cohen's *d* measured as the mean difference pre-post/mean SD of the difference.

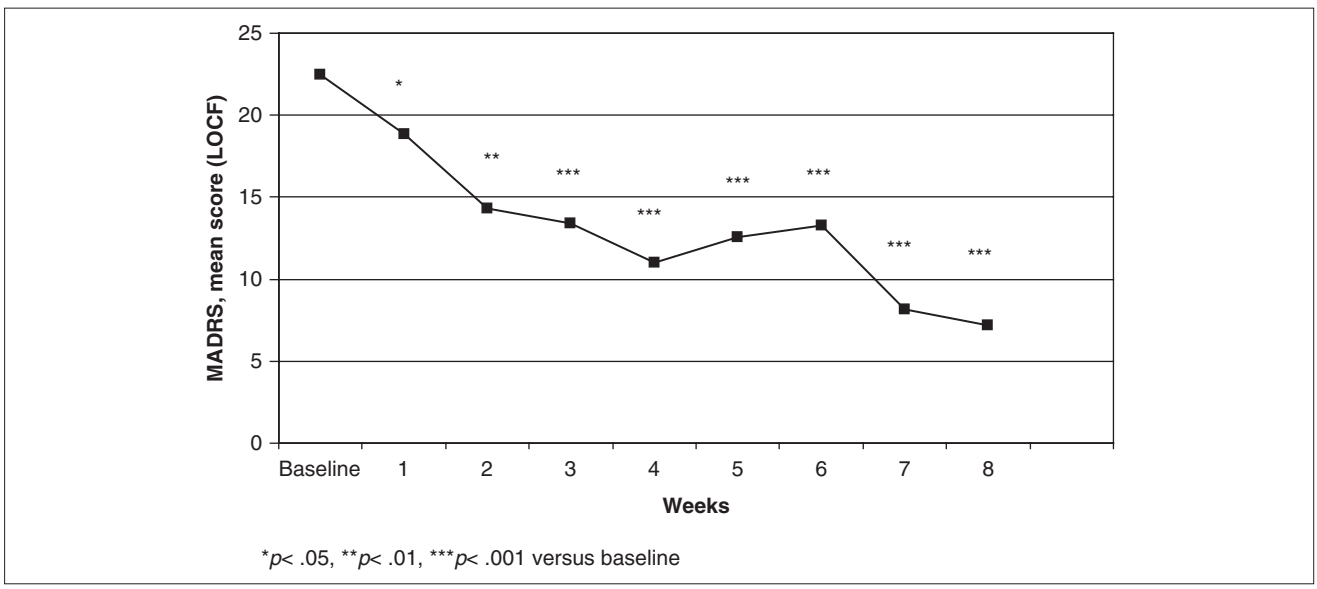

Figure 1. Change in the MADRS scores in 14 participants treated with EMP+ in open study over 8 weeks
Note: LOCF = last observation carried forward for missed visits.

in conjunction with improved ability to regulate anger. Although baseline scores were all within the normal range, mean change on these subscales was large (ES > .8) and equivalent to almost one standard deviation drop (or increase for regulation) from baseline (Table 2). A smaller change was noted in angry cognitions.

Compliance and Safety

The overall compliance rate was 97.2%; the lowest was at 89.3%. Ensuring compliance was a high priority of the trial. Pills were precounted and provided in 7 day boxes. At each visit, a new pill box (with pills precounted) was exchanged for the preceding week's box with any unused doses. Given that one symptom of ADHD is forgetfulness, all participants were offered three texts to their cell phones a day to remind them to take their pills. A total of 4 participants opted for the automatized texts. Two participants chose to decrease their daily dose half way through the trial: one to 10 and one to 12 pills per day as they decided that 15 a day was too high.

Two (14.3%) participants reported feeling nausea in the first few weeks of the trial but this problem dissipated when they were reminded always to take the pills with food. Four (28.6%) reported headaches in the first few weeks and one (7.1%) developed an itchy rash that cleared within 1 week although he had experienced a similar rash on one occasion before the trial. No other adverse events were reported.

Paired *t*-tests were used to examine whether there were any changes in hematology and biochemistry results. These analyses were based on 13 participants as one refused to do blood work. Two repeats (one baseline, one post-8 weeks) occurred on one hematological sample due to low white blood cells. The repeats both came back normal and these repeat values were used in the analyses. Even when using a liberal *p* value, there were only three significant changes in the group data: urate ($t(12) = 3.91$, $p < .001$; baseline: 0.31 (0.09), post 8-weeks 0.26 (0.07)); alkaline phosphatase ($t(12) = 2.24$, $p < .05$; baseline: 69.42 (18.99), post 8-weeks: 65.33 (20.221); and ferritin ($t(12) = 3.02$, $p < .01$; baseline: 142.92 (76.70), post 8-weeks: 118.77 (62.36)). However, the means at post 8-weeks were all within the normal range. There were no changes in any other variables, including glucose, lipids, white blood count, copper, and creatinine. Considering the identified side effects of antipsychotic medications and mood stabilizers (such as thrombocytopenia, leukopenia, agranulocytosis; Oyesanmi, Kunkel, Monti, & Field, 1999) and raised glucose levels (Scheen & De Hert, 2007), this *lack* of difference in fasting glucose, lipids, white blood cell count, and neutrophils is important. Furthermore, this overall lack of change in hematology and biochemistry is consistent with reports from other researchers.

Natural Remission of Symptoms Pre-Trial

As a number of the participants had been recruited from other studies, we were able to look at measures that had been repeated to verify whether the changes observed in the trial were a consequence of the natural progression of conditions to get better over time, regardless of the intervention. In effect, these measures represent a natural multiple baseline design. Using only those participants for whom we had repeated measures and where the informant remained the same ($n = 4$), there was no significant change in scores over time (varying from 1 month to 11 months prebaseline). The self-report scores on the CAARS (DSM scales) and MADRS scores either remained the same or became marginally worse over time, and the observer reports also showed moderate worsening over time.

Natural Follow-Up

At the end of the 8 weeks, if participants expressed an interest, they were informed about how to obtain the micronutrient formula. All participants consented to be contacted approximately 2 months follow up regardless of whether they stayed on EMP+. Contact varied from 2 to 6 months post-trial. Participants who had been on EMP+ for at least 2 months post trial were compared with those who had been off it for at least 2 months. One participant who came off did not complete the follow-up assessment.

Across all primary outcome measures, the means at follow-up were lower for those who stayed on ($n = 7$) compared with those who stopped EMP+ ($n = 6$). This is in contrast with scores at the end of the trial where there were no differences between these two groups. Further inspection of the data indicated that on average, those participants who stayed on either generally maintained change or continued to improve whereas those who came off showed some maintenance of symptoms or regression in symptoms over time although they did not go back to baseline. Table 1 shows the individual MADRS and CAARS scores on the DSM subscales and Figure 2 shows the mean CAARS scores for both self and observer across the three assessment periods.

One participant, who initially chose to stop taking the formula, decided after a 2 month period to resume EMP+ due to worsening of symptoms during that time. Two of those who stopped the formula chose to do so in order to try a psychostimulant to help with concentration problems. Interestingly, three of those who stopped had lower baseline depression scores and were more likely to be inattentive ADHD. Other possible positive benefits identified included 2 participants on EMP+ who successfully quit smoking and two participants, who entered the trial with severe OCD, were in remission by the end of the trial.

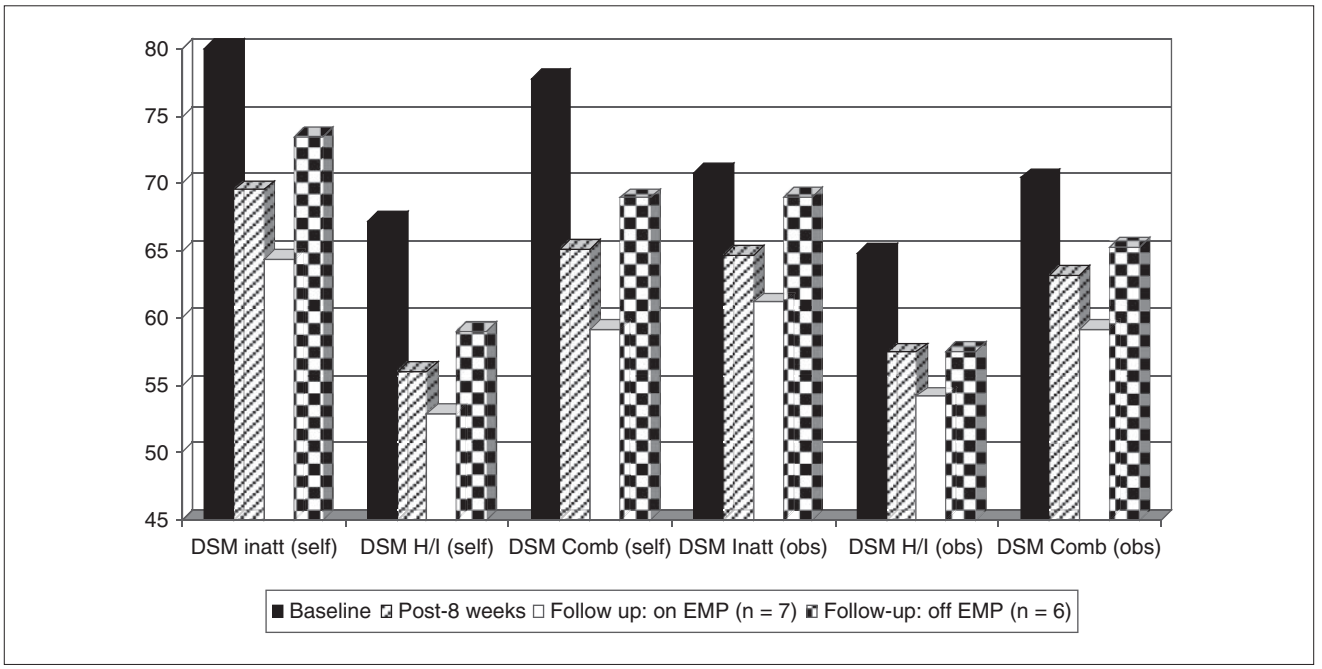

Figure 2. CAARS DSM based scales (both self and observer) across the three assessment periods
Note: Inatt = inattention; H/I = hyperactivity/impulsivity; comb = combined; obs = observer.

Discussion

This study investigated the effect of a micronutrient supplement on ADHD and mood symptoms in an 8-week open label trial. Changes in all areas of functioning were large and significant. Indeed, the changes in ADHD symptoms recorded here were equivalent or larger than those reported from conventional treatments like methylphenidate (Medori et al., 2008) or atemoxetine [Reimherr et al., 2005] in adult samples. Furthermore, the changes on the MADRS [10 (83.3%) of the 12 participants who entered the trial with clinically elevated symptoms of depression showed a 50% reduction in symptoms post 8-weeks] are again equivalent or better than published studies using antidepressants [e.g., carbamazapine (Zhang et al., 2008) and venlafaxine/fluoxetine (Costa e Silva, 1998; Nemeroff & Thase, 2007) and cognitive-behavioral and interpersonal therapy (Luty et al., 2007)]. Furthermore, this study also replicates other international studies showing the benefit of EMP+ in the treatment of mental illness. The treatment had also remarkably few side effects in comparison to many of the antidepressant and stimulant regimes. For example, although there were only a few participants who had a history of manic symptoms, the treatment did not activate mania in them or any other participants, a concern for some antidepressants (Morishita & Arita, 2005).

Many studies do not evaluate a number of different conditions within the same study to assess the effect of a treatment; it is therefore clinically relevant that we chose a more complex group of participants and found improvements across a wide range of symptoms, such as stress levels, anxiety, aggression, anger control, and quality of life. It is possible that these other improvements were due to a halo effect, which is when improvement in one area of functioning (such as depression) resulted in a perceived improvement in another area of functioning. However, positive changes were also reflected in the observer reports, a finding not always seen when self and clinician reports document improvement. Based on meetings with some of these observers, they were typically initially sceptical of the likely effectiveness of this treatment approach.

We chose to report on *T* scores so that the clinical relevance could more easily be determined. As such, although all effect sizes were large for the primary outcome measures, the *DSM* inattentive scores remained in the clinical range whereas the hyperactive/impulsive and emotional lability scores reduced to the normal nonclinical range. These specific areas where more improvement was noted were generally consistent between self and observer reports although self-reported changes were larger than observer-reported changes. Perhaps the participants were influenced by expectancy effects; equally they may be more aware of change given that they are reporting on their own internal experiences. Continued problems with concentration were also observed on the MADRS concentration item whereby

participants continued to report problems in this area, despite improved mood.

While these data cannot be used as evidence of efficacy, there are scientific reasons why such an approach is worthy of further investigation. Minerals, vitamins, and amino acids are critical to the synthesis of neurotransmitters and often are required *in combination* for optimal benefit. Although single ingredients contained in EMP+ have been identified as being deficient in some people with ADHD (e.g., zinc; Arnold et al., 2005; magnesium; Starobrat-Hermelin, 1998) and single ingredients have been found helpful in the treatment of ADHD, single nutrient approaches may not be sufficient to correct all imbalances due to the array of nutrients required for effective neurochemical synthesis (Mertz, 1994). Kaplan et al. (2007) speculate that some forms of mental dysfunction may be caused by in-born errors of metabolism in key neurobiological pathways, in particular those responsible for neurochemical synthesis, second messenger signaling and uptake of neurotransmitters. Ames, Elson-Schwab, and Silver (2002) demonstrated that genetic diseases can reduce the binding affinity of enzymes, which in turn lowers the rate of metabolic reactions, resulting in deficiencies. As micronutrients function as cofactors in enzymatic reactions responsible for synthesizing and metabolizing neurotransmitters, if they are deficient, then overall synthesis of neurotransmitters will be lower. It may be that only a broad-based micronutrient formula can correct and stabilize all these functions, particularly in cases that have been resistant to other forms of treatment (Gately & Kaplan, 2009). Recent studies also suggest that the manufacture of adenosine triphosphate (ATP) is compromised in ADHD, bipolar disorder and other mental disorders (Russell et al., 2006; Young, 2007). It is possible that micronutrients influence mitochondrial activity through increasing ATP and thereby improving psychiatric symptoms.

Nutrient content of our food supply could also be considered in conjunction with these hypotheses. Data are indicating that the mineral and trace elements of fruits and vegetables have been decreasing significantly over the past 50 years (Ekholm et al., 2007; Mayer, 1997), at least partially as a result of the poor remineralization of the soil. It is possible that some individuals are also highly sensitive to these nutritional depletions present in food as their biochemical needs are different. New Zealand, in particular, has depleted levels of important trace minerals such as selenium (Thomson & Robinson, 1980).

It is interesting that the effect on attention was smaller than the effect on hyperactivity and impulsivity. Many researchers have argued that these two dimensions are distinguishable, showing different response styles to tasks (Derefinko et al., 2008), different genetic profiles (Rowe, Stever, & Gard, 1998), and different associated features such as co-occurring disorders (Nigg, 2000). There is also evidence that those individuals with mainly inattentive problems may be less likely to respond to methylphenidate (Barkley, 2001). Response inhibition is often viewed as more strongly linked to the hyperactive-impulsive symptoms (O'Driscoll et al., 2005). Although detailing mechanisms is beyond the scope of this article, it is possible that EMP+ is having a greater effect on the chemical pathways involved in inhibition, impulsivity, hyperactivity, and mood regulation than inattention, thus providing further evidence for the distinction between these two dimensions of ADHD behavior. In particular, EMP+ may influence neurochemical regulation hypothesized to be compromised in individuals affected with ADHD, such as striatal and prefrontal dopamine projections involved in reward systems and pleasurable affective states (Sagvolden, Aase, Johansen, & Russell, 2005). It is also possible that it takes longer to correct the nutrient deficiencies involved in the regulation of attention, and that 8 weeks is not sufficient. It is also possible that improvement in mood resulted in the improvements noted in other areas of functioning, such as ADHD. Longer term studies and more homogenous samples (such as purely ADHD) are necessary to establish this.

This type of trial is limited by the open-label design. As such, we cannot confidently attribute change to the consumption of the pills given the robustness of the placebo effect (Wampold, Imel, & Minami, 2007). Indeed, other observations were made that may explain some of the positive effects over time. For example, many participants commented that the strict pill taking regimen "forced" them into a better daily routine of getting out of bed, eating regular meals, drinking plenty of water and attending to themselves more actively than they would have otherwise. Given that these variables are well known to influence mood, they could have contributed to the overall positive effect. Indeed, dehydration is known to negatively affect cognitive function (Cian et al., 2000). Furthermore, the group was largely motivated, self-referred and open to a natural treatment for their mental illness. This sample is therefore more likely to show positive change compared with the larger psychiatric community. Certainly, the fact that there wasn't full regression to baseline for those who stopped EMP+ suggests that there was greater control of symptoms following the end of the trial. It is also possible that a 2 month follow-up was not long enough for a reversal to occur. There are also limitations to generalizability to the wider ADHD population—this sample consisted of people with both ADHD and mood dysregulation, as such we do not know if the micronutrients would be beneficial for those with only ADHD or ADHD and other coexisting problems such as antisocial behaviors or drug and alcohol dependence. Further studies on subtypes would be necessary to better understand the extent this approach would be helpful for ADHD more generally. Based on these preliminary observations, it is possible that this intervention is less helpful for those with ADHD, Predominantly

Inattentive Type with no co-occurring conditions. However, given that complex presentations to clinics are the norm rather than the exception, these results may prove to be more relevant to patients referring to clinics.

Participation in trials is also known to artificially inflate the effect of a treatment due to the care provided, the weekly contact, the therapeutic input, and the external assistance provided to ensure treatment compliance was optimized. Patient–practitioner relationships have been found to be one of the most robust factors contributing to the placebo effect (Kaptchuk et al., 2008). Attempts were made to keep appointments short and minimal, focus on review of symptoms only and not engage in substantial discussions about strategies to deal with symptoms. Furthermore, given that the population chosen was more complex than typical trial participants (based on the presence of co-occurring disorders and self-report of poor response to previous therapies), the response rate tends to be lower for such individuals. Also, placebo effects tend to be smaller with more moderate levels of depression (Khan, Leventhal, Khan, & Brown, 2002)—given that 11 participants (78.6%) had moderate levels of depression (defined as scores between 18 and 34 on the MADRS (Müller, Szegedi, Wetzel, & Benkert, 2000), the placebo effect is less likely to fully explain the substantial changes observed. In addition, the fact that changes were maintained and even further improved after the trial suggests that therapist contact was not the only factor involved in symptom remission.

It is also possible that the change was not due to the pills but due to natural remission of symptoms over time. While this explanation cannot be ruled out, there are a few reasons why it may not be the case. First, we looked at the data on a few participants prior to the trial and none of those people showed natural remission. One participant who chose to stop the formula for 8 weeks and then return to it showed symptom control while on and symptom return while off. By coincidence, slightly more participants (57%) started the trial in the summer and ended in the winter when symptoms would be expected to get worse.

While this pilot study does not establish efficacy, the data are compelling enough to warrant replication and controlled studies to better elucidate the changes that may be occurring. If the preference for improvement in hyperactive-impulsive and affective symptoms is replicated in larger trials, then investigations using neurocognitive tests believed to be sensitive to deficits associated with these behaviors would be warranted. Other populations with impulsive problems could be trialed, such as gamblers, people with OCD or Borderline Personality Disorder. fMRI and other mapping techniques could assist with identifying change associated with treatment as well as documenting possible mechanisms of action of EMP+ on neural circuitry.

Acknowledgments

We thank the University of Canterbury for its on-going research support, Drs. Katharine Shaw and Chris Florkowski for their medical input on interpreting the blood tests, and Rachel Harrison and Jeni Johnstone for their assistance with data management. Most importantly, we thank the participants who took the chance to try an experimental treatment for their mental illness, David Hardy and Tony Stephan whose original observations led to the development of this research and to Synergy Group of Canada Inc. for providing the formula for the duration of the trial.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interests with respect to their authorship or the publication of this article.

Funding

The authors received financial support from the Department of Psychology, University of Canterbury.

Note

1. EMPowerplus is distributed by TruehopeNutritional Support. It consists of 36 ingredients: 14 vitamins, 16 minerals, 3 amino acids and 3 antioxidants. A list of the ingredients can be found on the company's website, Truehope.com.

References

Akhondzadeh, S., Mohammadi, M.-R., & Khademi, M. (2004). Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: A double blind and randomized trial. *BMC Psychiatry, 4*, 9.

Almeida Montes, L. G., Hernandez Garca, A. O., & Ricardo-Garcell, J. (2007). ADHD prevalence in adult outpatients with nonpsychotic psychiatric illnesses. *Journal of Attention Disorders, 11*, 150-156.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: Author.

Ames, B. N., Elson-Schwab, I., & Silver, E. (2002). High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased Km): Relevance to genetic disease and polymorphisms. *American Journal of Clinical Nutrition, 75*, 616-658.

Arnold, L. E. (1999). Treatment alternatives for attention-deficit/hyperactivity disorder (ADHD). *Journal of Attention Disorders, 3*, 30-48.

Arnold, L. E., Amato, A., Bozzolo, H., Hollway, J., Cook, A., Ramadan, Y., et al. (2007). Acetyl-l-carnitine in attention-deficit/hyperactivity disorder: A multi-site, placebo-controlled pilot trial. *Journal of Child and Adolescent Psychopharmacology, 17*, 791-801.

Arnold, L. E., Bozzolo, H., Hollway, J., Cook, A., DiSilvestro, R. A., Bozzolo, D. R., et al. (2005). Serum zinc correlates with

parent- and teacher-rated inattention in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology, 15*, 628-636.

Barkley, R. A. (1997). Behavioral inhibition, sustained attention, and executive functions: Constructing a unifying theory of ADHD. *Psychological Bulletin, 121*, 65-94.

Barkley, R. A. (2001). The inattentive type of ADHD as a distinct disorder: What remains to be done. *Clinical Psychology: Science and Practice, 8*, 489-493.

Baroni, A., Lunsford, J. R., Luckenbaugh, D. A., Towbin, K. E., & Leibenluft, E. (2009). Practitioner review: The assessment of bipolar disorder in children and adolescents. *Journal of Child Psychology and Psychiatry, 50*, 203-215.

Baumgaertel, A. (1999). Alternative and controversial treatments for attention-deficit/hyperactivity disorder. *Pediatric Clinics of North America, 46*, 977-992.

Biederman, J., Mick, E., Surman, C., Doyle, R., Hammerness, P., Harpold, T., et al. (2006). A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 59*, 829-835.

Bilici, M., Yildirim, F., Kandil, S., Bekaroglu, M., Yildirmis, S., Deger, O., et al. (2004). Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 28*, 181-190.

Cian, C., Koulmann, N., Barraud, P. A., Raphel, C., Jimenez, C., & Melin, B. (2000). Influences of variations in body hydration on cognitive function: Effect of hyperhydration, heat stress, and exercise-induced dehydration. *Journal of Psychophysiology, 14*, 29-36.

Conners, C. K., Erhardt, D., & Sparrow, M. A. (2003). Conners' Adult ADHD Rating Scales (CAARS). *Archives of Clinical Neuropsychology, 18*, 431-437.

Costa e Silva, J. (1998). Randomized, double-blind comparison of venlafaxine and fluoxetine in outpatients with major depression. *Journal of Clinical Psychiatry, 59*, 352-357.

Derefinko, K. J., Adams, Z. W., Milich, R., Fillmore, M. T., Lorch, E. P., & Lynam, D. R. (2008). Response style differences in the inattentive and combined subtypes of attention-deficit/hyperactivity disorder. *Journal of Abnormal Child Psychology, 36*, 745-758.

Ekholm, P., Reinivuo, H., Mattila, P., Pakkala, H., Koponen, J., Happonen, A., et al. (2007). Changes in the mineral and trace element contents of cereals, fruits and vegetables in Finland. *Journal of Food Composition and Analysis, 20*, 487-495.

Epstein, J., Johnson, D., & Conners, C. (2002). *Conners' adult ADHD diagnostic interview for DSM-IV (CAADID): Technical manual*. New York: MHS.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). *Structured clinical interview for DSM-IV-TR axis i disorders, research version* (Patient ed.). New York: Biometrics Research, New York State Psychiatric Institute.

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

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

Gualtieri, C. L., Ondrusek, M. G., & Finley, C. (1985). Attention deficit disorders in adults. *Clinical Neuropharmacology, 8*, 343-356.

Hawley, C. J., Gale, T. M., & Sivakumaran, T. (2002). Defining remission by cut off score on the MADRS: selecting the optimal value. *Journal of Affective Disorders, 72*, 177-184.

Kaplan, B. J., Crawford, S. G., Field, C. J., & Simpson, J. S. (2007). Vitamins, minerals, and mood. *Psychological Bulletin, 133*, 747-760.

Kaplan, B. J., Crawford, S. G., Gardner, B., & Farrelly, G. (2002). Treatment of mood lability and explosive rage with minerals and vitamins: Two case studies in children. *Journal of Child and Adolescent Psychopharmacology, 12*, 205-219.

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

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

Kaptchuk, T. J., Kelley, J. M., Conboy, L. A., Davis, R. B., Kerr, C. E., Jacobson, E. E., et al. (2008). Components of placebo effect: Randomised controlled trial in patients with irritable bowel syndrome. *British Medical Journal, 336*, 999-1003.

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., et al. (2006). The prevalence and correlates of adult ADHD in the United States: Results from the national comorbidity survey replication. *American Journal of Psychiatry, 163*, 716-723.

Khan, A., Leventhal, R. M., Khan, S. R., & Brown, W. A. (2002). Severity of depression and response to antidepressants and placebo: An analysis of the food and drug administration database. *Journal of Clinical Psychopharmacology, 22*, 40-45.

Kolar, D., Keller, A., Golfinopoulos, M., Cumyn, L., Syer, C., & Hechtman, L. (2008). Treatment of adults with attention-deficit/hyperactivity disorder. *Neuropsychiatric Disease and Treatment, 4*, 389-403.

Leon, A. C., Solomon, D. A., Mueller, T. I., Endicott, J., Posternak, M., Judd, L. L., et al. (2000). A brief assessment of psychosocial functioning of subjects with bipolar I disorder: The LIFE-RIFT. Longitudinal interval follow-up evaluation-range impaired functioning tool. *Journal of Nervous and Mental Disease, 188*, 805-812.

Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the Depression Anxiety Stress Scales* (2nd ed.). Sydney: Psychology Foundation.

Luty, S. E., Carter, J. D., McKenzie, J. M., Rae, A. M., Frampton, C. M. A., Mulder, R. T., et al. (2007). Randomised controlled trial of interpersonal psychotherapy and cognitive-behavioural therapy for depression. *British Journal of Psychiatry, 190*, 496-502.

Mattes, J. A., Boswell, L., & Oliver, H. (1984). Methylphenidate effects on symptoms of attention deficit disorder in adults. *Archives of General Psychiatry, 41*, 1059-1063.

Mayer, A. B. (1997). Historical changes in the mineral content of fruits and vegetables. *British Journal of Food, 99*, 207-211.

Medori, R., Ramos-Quiroga, J. A., Casas, M., Kooij, J. J. S., Niemela, A., Trott, G.-E., et al. (2008). A randomized, placebo-controlled trial of three fixed dosages of prolonged release OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 63*, 981-989.

Mertz, W. (1994). A balanced approach to nutrition for health: The need for biologically essential minerals and vitamins. *Journal of the American Dietetic Association, 94*, 1259-1262.

Montgomery, S. A., & Asberg, M. (1979). A new depression scale designed to be sensitive to change. *British Journal of Psychiatry, 134*, 382-389.

Morishita, S., & Arita, S. (2005). Clinical characteristics as predictors of response to fluvoxamine, paroxetine and milnacipran in patients with depression. *Current Psychiatry Reviews, 1*, 319-324.

Müller, M. J., Szegedi, A., Wetzel, H., & Benkert, O. (2000). Moderate and severe depression: Gradations for the Montgomery-Åsberg Depression Rating Scale. *Journal of Affective Disorders, 60*, 137-140.

Nemeroff, C. B., & Thase, M. E. (2007). A double-blind, placebo-controlled comparison of venlafaxine and fluoxetine treatment in depressed outpatients. *Journal of Psychiatric Research, 41*, 351-359.

Nemzer, E. D., Arnold, L. E., Votolato, N. A., & McConnell, H. (1986). Amino acid supplementation as therapy for attention deficit disorder. *Journal of the American Academy of Child Psychiatry, 25*, 509-513.

Nigg, J. T. (2000). On inhibition/disinhibition in developmental psychopathology: Views from cognitive and personality psychology and a working memory taxonomy. *Psychological Bulletin, 126*, 200-246.

Nigg, J. T. (2001). Is ADHD a disinhibitory disorder? *Psychological Bulletin, 127*, 571-598.

Novaco, R. W. (2003). *The Novaco Anger Scale and Provocation Inventory (NAS-PI)*. Los Angeles: Western Psychological Services.

O'Driscoll, D. A., Depatie, L., Holahan, A. V., Savion-Lemieux, T., Barr, R. G., Jolicoeur, C., et al. (2005). Executive functions and methylphenidate response in subtypes of attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*, 1452-1460.

Oyesanmi, O., Kunkel, E. J. S., Monti, D. A., & Field, H. L. (1999). Hematologic side effects of psychotropics. *Psychosomatics: Journal of Consultation Liaison Psychiatry, 40*, 414-421.

Polanczyk, G., de Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: A systematic review and meta-regression analysis. *American Journal of Psychiatry, 164*, 942-948.

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

Reimherr, F. W., Marchant, B. K., Strong, R. E., Hedges, D. W., Adler, L., Spencer, T. J., et al. (2005). Emotional dysregulation in adult ADHD and response to atomoxetine. *Biological Psychiatry, 58*, 125-131.

Reimherr, F. W., Wender, P. H., Wood, D. R., & Ward, M. (1987). An open trial of {l}-tyrosine in the treatment of attention deficit disorder, residual type. *American Journal of Psychiatry, 144*, 1071-1073.

Rowe, D. C., Stever, C., & Gard, J. M. C. (1998). The relation of the dopamine transporter gene (DAT1) to symptoms of internalizing disorders in children. *Behavior Genetics, 28*, 215-225.

Rucklidge, J. J. (2009). Successful treatment of OCD with a micronutrient supplement following partial response to Cognitive Behavioral Therapy (CBT): A case study. *Journal of Anxiety Disorders, 23*, 836-840.

Rucklidge, J. J., Johnstone, J., & Kaplan, B. J. (2009). Nutrient supplementation approaches in the treatment of ADHD. *Expert Review of Neurotherapeutics, 9*, 461-476.

Rucklidge, J. J., & Kaplan, B. J. (1997). Psychological functioning of women identified in adulthood with attention-deficit/hyperactivity disorder. *Journal of Attention Disorders, 2*, 167-176.

Russell, V. A., Oades, R. D., Tannock, R., Killeen, P. R., Auerbach, J. G., Johansen, E. B., et al. (2006). Response variability in attention-deficit/hyperactivity disorder: A neuronal and glial energetics hypothesis. *Behavioral and Brain Function, 2*, 23.

Sagvolden, T., Aase, H., Johansen, E. B., & Russell, V. A. (2005). A dynamic developmental theory of attention-deficit/hyperactivity disorder (ADHD) predominantly hyperactive/impulsive and combined subtypes. *Behavioral and Brain Sciences, 28*, 397-468.

Scheen, A. J., & De Hert, M. A. (2007). Abnormal glucose metabolism in patients with antipsychotics. *Diabetes and Metabolism, 33*, 169-175.

Simmons, M. (2003). Nutritional approach to bipolar disorder. *Journal of Clinical Psychiatry, 64*, 338-338.

Skirrow, C., McLoughlin, G., Kuntsi, J., & Asherson, P. (2009). Behavioral, neurocognitive and treatment overlap between attention-deficit/hyperactivity disorder and mood instability. *Expert Review of Neurotherapeutics, 9*, 489-503.

Spearing, M. K., Post, R. M., Leverich, G. S., Brandt, D., & Nolen, W. (1997). Modification of the clinical global impressions (CGI) scale for use with bipolar illness (BP): The CGI: BP. *Psychiatry Research, 73*, 159-171.

Spencer, T., Biederman, J., Wilens, T., Doyle, R., Surman, C., Prince, J., et al. (2005). A Large, double-blind, randomized clinical trial

of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry, 57*, 456-463.

Starobrat-Hermelin, B. (1998). The effect of deficiency of selected bio-elements on hyperactivity in children with certain specified mental disorders. *Annales Academiae Medicae Stetinensis, 44*, 297-314.

Starobrat-Hermelin, B., & Kozielec, T. (1997). The effects of magnesium physiological supplementation on hyperactivity in children with attention deficit hyperactivity disorder (ADHD). Positive response to magnesium oral loading test. *Magnesium Research, 10*, 149-156.

Thomson, C. D., & Robinson, M. F. (1980). Selenium in human health and disease with emphasis on those aspects peculiar to New Zealand. *The American Journal of Clinical Nutrition, 33*, 303-323.

Torgersen, T., Bjervan, B., & Rasmussen, K. (2008). Treatment of adult ADHD: Is current knowledge useful for clinicians? *Neuropsychiatric Disease and Treatment, 4*, 177-186.

Umphress, V. J., Lambert, M. J., Smart, D. W., Barlow, S. H., & Clouse, G. (1997). Concurrent and construct validity of the outcome questionnaire. *Journal of Psychoeducational Assessment, 15*, 40-55.

Van Oudheusden, L. J., & Scholte, H. R. (2002). Efficacy of carnitine in the treatment of children with attention-deficit hyperactivity disorder. *Prostaglandins, Leukotrienes, and Essential Fatty Acids, 67*, 33-38.

Wampold, B. E., Imel, Z. E., & Minami, T. (2007). The placebo effect: "Relatively large" and "robust" enough to survive another assault. *Journal of Clinical Psychology, 63*, 401-403.

Wood, D. R., Reimherr, F. W., & Wender, P. H. (1985). Treatment of attention deficit disorder with DL-phenylalanine. *Psychiatry Research, 16*, 21-26.

Wynne, A., McCartney, A., Brostoff, J., Hudspith, B., & Gibson, G. (2004). An in vitro assessment of the effects of broad-spectrum antibiotics on the human gut microflora and concomitant isolation of a Lactobacillus plantarum with anti-Candida activities. *Anaerobe, 10*, 165-169.

Young, L. T. (2007). Is bipolar disorder a mitochondrial disease? *Journal of Psychiatry and Neuroscience, 32*, 160-161.

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: Reliability, validity, and sensitivity. *British Journal of Psychiatry, 133*, 429-435.

Zhang, Z.-J., Tan, Q.-R., Tong, Y., Li, Q., Kang, W.-H., Zhen, X.-C., et al. (2008). The effectiveness of carbamazepine in unipolar depression: A double-blind, randomized, placebo-controlled study. *Journal of Affective Disorders, 109*, 91-97.

Bios

Julia Rucklidge, PhD, is an Associate Professor and Clinical Psychologist in the Department of Psychology at the University of Canterbury. She is also director of the ADHD Diagnostic Assessment and Research Unit.

Mairin Taylor is a PhD student in the Department of Psychology at the University of Canterbury and is studying risk taking behaviors in adults with ADHD.

Kathryn Whitehead, MA, is a Clinical Psychologist who works at the Mothers and Babies Inpatient Unit at the Canterbury District Health Board. She specializes in adolescent, maternal, and infant mental health.