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Moderators of treatment response in adults with ADHD treated with a vitamin–mineral supplement☆

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ABSTRACT

Background: To date there has been no research investigating moderators of response to micronutrient treatment of mental illness, specifically baseline nutrient levels.
Method: We conducted analyses of data from a randomized placebo-controlled trial (RCT) of 80 adults (≥16 years) with Attention-Deficit/Hyperactivity Disorder (ADHD), whereby participants were treated acutely (8 weeks) with micronutrients or placebo followed by an open-label (OL) phase of 8 weeks whereby all participants received micronutrients. To ensure that all participants had been exposed to the micronutrients for 8 weeks, only those 64 who had adhered to the treatment protocol and completed 8 weeks on nutrients were included in the data analysis: 34 from the group that had been randomized to the micronutrient arm, and 30 from the group that had been randomized to the placebo group and hence had only received nutrients in the OL phase. Six outcomes were examined: change in ADHD symptoms (self/clinician), ADHD responder, Clinical Global Impression-Improvement (CGI-I), change in mood, and change in Global Assessment of Functioning (GAF). Demographic, developmental and psychiatric history, current clinical characteristics, and baseline nutrient levels were all considered as putative predictors.
Results: There were significant changes in all outcome variables after 8 weeks exposure to the micronutrients. Among the nutrients recorded at baseline, substantial deficiencies (27%) were only observed for vitamin D. However, other than an association showing that higher iron at baseline was correlated with higher baseline depression scores, baseline nutrient levels were not correlated with baseline psychiatric variables/current clinical characteristics. Regression analyses revealed that *higher* baseline ferritin and *lower* baseline copper and vitamin D levels were associated with a better response to treatment for some but not all outcomes. None of the other nutrient levels was found to be associated with outcome, including zinc, vitamin B_{12}, iron, and folate. There were no childhood risk factors, demographic variables or clinical correlates that contraindicated micronutrient treatment; more severe symptoms at baseline and greater number of developmental risk factors predicted greater treatment response.
Conclusions: Further research looking at nutrients more broadly is required to confirm these initial observations about ferritin, vitamin D and copper; however, the results suggest that serum nutrient levels have limited value for identifying who will respond to treatment.

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) in adulthood has become increasingly recognized as an important disorder to treat, with prevalence rates for adult ADHD estimated between 4 and 5% (Kessler et al., 2006) and poor long-term outcomes documented for those followed to adulthood (Klein et al., 2012). Predictors of treatment response are confined to medication trials with symptom severity, gender, co-occurring disorders, and academic achievement shown to influence outcome (Buitelaar et al., 2011; Torgersen et al., 2008). The most common risk factors studied are genetic; however, this emphasis has led to an overall neglect in considering the role that the environment

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; CAARS, Conners' Adult ADHD Rating Scales; MADRS, Montgomery–Åsberg Depression Rating Scale; GAF, Global Assessment of Functioning; CGI-I, Clinical Global Impression-Improvement; NZSEI, New Zealand Socio-Economic Index; RCT, Randomized Controlled Trial; OL, Open Label; EMP, EMPowerplus; CAADID, Conners' Adult ADHD Diagnostic Interview for DSM-IV; K-SADS, Kiddie-Schedule for Affective Disorders and Schizophrenia; DSM-IV, Diagnostic and Statistical Manual 4th Edition; SCID-I, Structured Clinical Interview for DSM-IV-TR Axis I Disorders; NIMH, National Institute of Mental Health; RdoC, Research Domain Criteria.

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might play in the expression of the symptoms (Calarge et al., 2010). Although there has been a recent interest in the role that nutrients play in the expression and treatment of ADHD (Milte et al., 2012; Nigg et al., 2012), as well as studies showing associations between nutrient levels and ADHD behaviours (Arnold et al., 2005), to date no study on broad-based micronutrient supplementation has investigated whether nutrient levels can be useful at predicting treatment response.

Biochemical markers or biomarkers are becoming increasingly studied in attempts to identify those who might be at risk for ADHD as well as to identify possible areas for intervention (Scassellati et al., 2012). Some biomarkers are modifiable and thus may lead to targeted treatments. Individual nutrients have been the focus of studies attempting to determine the role that they may play in the expression of ADHD in children. The most studied candidates have been iron and zinc, with some positive and some negative results (Akhondzadeh et al., 2004; Arnold et al., 2011; Bilici et al., 2004; Cortese et al., 2009; Konofal et al., 2008; Oner and Oner, 2008; Oner et al., 2010; Sever et al., 1997; Uckardes et al., 2009). The rationale for supplementing with these nutrients includes the role that iron plays as a coenzyme of tyrosine hydroxylase, critical for dopamine synthesis (Oner and Oner, 2008), and the role that zinc plays in regulating the dopamine transporter, among its many functions (Lepping and Huber, 2010). There have been no studies looking at the impact of nutrient levels on the expression of ADHD in adults. Nutrient biomarkers seem a potentially profitable way forward to predict treatment responders, given that mechanisms by which nutrient treatments might work implicate nutrients working at the cellular level, either through improving mitochondrial functioning (Gardner and Boles, 2005), correcting in-born errors of metabolism (Kaplan et al., 2007), possibly addressing compromised gastrointestinal functioning (Jackson et al., 2012) or inflammation (Donev and Thome, 2010), or acting as cofactors for various metabolic activities in the body (Ames et al., 2002). Deficiencies in nutrients in particular may identify individuals who may benefit from micronutrient treatment.

This study presents the first investigation looking at whether nutrient biomarkers taken prior to a broad-based micronutrient treatment are useful for predicting treatment response in adults with ADHD. These predictors were explored alongside more common predictors such as demographic variables, developmental history, and clinical correlates (Buitelaar et al., 2011; Torgersen et al., 2008). This study aligns well with the National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC), which encourages research that aims to uncover laboratory-based evaluations that can assist with prognosis and treatment (Insel et al., 2010).

2. Methods

2.1. Study design

The study received ethical approval from both the National Upper South A Health and Disability Ethics Committee and the Human Ethics Committee at the University of Canterbury. After describing the experimental nature of the trial and explaining the other treatment options available in the community, written informed consent was obtained from all participants. The trial was prospectively registered (ACTRN12609000308291).

Study details have been described previously (Rucklidge et al., in press). In brief, this was an 8 week double-blind (participants and investigators), parallel-group randomized controlled trial (RCT) designed to assess the efficacy and safety of a broad spectrum micronutrient formula (EMPowerplus (EMP)) compared with placebo followed by an 8 week open-label (OL) trial with EMP in medication-free men and women with ADHD, 16 years and older. Participants had to meet criteria for ADHD based on the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID (Epstein et al., 2002)) or, for those under 18 years (n = 7), the Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (Kaufman et al., 1997). In addition, participants had to have an elevated level (T score > 65) on one or more of the three DSM-IV subscales of the Conners' Adult ADHD Rating Scales (CAARS (Conners et al., 2003)) on either the self or the observer versions. For participants under 18 years, the Conners' Rating Scales for youth and parents were completed (Conners, 1997). Comorbidity was assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version (SCID-I (First et al., 2002)). The SCID-I was also used to verify whether ADHD symptoms being reported were better attributed to another Axis I disorder. Information on historical symptoms was obtained for all participants either directly from the participants if possible or from reviewing past psychological assessments or report cards (if available) or interviewing family members for supporting information.

Participants took 5 capsules per day initially, divided into three doses to be taken with meals and water, increasing to 10 capsules per day after 3 days, divided into three doses. On the 7th day, the dose was further increased to 15 capsules per day, in 3 doses of 5 capsules. The placebo and EMP (see Table 1 for EMP ingredients) were identical in appearance, used the same coating, and the placebo included riboflavin in order to mimic the smell and change in urine colour associated with taking vitamins. Following the 8-week double-blind RCT phase, participants could chose to enter an 8-week OL phase using EMP (n = 69). The titration regimen used at the start of the RCT was used again for all participants at the beginning of the OL phase.

At baseline, trial completion and post-OL, laboratory blood screening tested thyroid functions, serum lipids, prolactin, fasting glucose, blood clotting, iron, zinc, vitamin D, vitamin B_{12} and copper levels. Urinalysis and urine drug screen were also undertaken. These data were reviewed by the study physician. Safety data including laboratory values and

Table 1
Ingredients of EMPowerplus™ with recommended daily allowances (RDA) for adults given in the same unit.

EMP ingredients	15 capsules	Male RDA	Female RDA
Vitamin A	5760 IU	3000	2333
Vitamin C	600 mg	90	75
Vitamin D	1440 IU	600	600[b]
Vitamin E	360 IU	22.5	22.5
Thiamin	18 mg	1.2	1.1
Riboflavin	13.5 mg	1.3	1.1
Niacin	90 mg	16	14
Vitamin B6	36 mg	1.3	1.3[b]
Folic acid	1440 μg	400	400
Vitamin B12	900 μg	2.4	2.4
Biotin	1080 μg	30	30[a]
Pantothenic acid	21.6 mg	5	5[a]
Calcium	1320 mg	1000	1000[b]
Iron	13.7 mg	8	18[b]
Phosphorus	840 mg	700	700
Iodine	204 μg	150	150
Magnesium	600 mg	400	310[b]
Zinc	48 mg	11	8
Selenium	204 μg	55	55
Copper	7.2 mg	0.9	0.9
Manganese	9.6 mg	2.3	1.8[a]
Chromium	624 μg	35	25[ab]
Molybdenum	144 μg	45	45
Potassium	240 mg	4700	4700[a]
Choline bitartrate	540 mg	550	425[a]
dl-Phenylalanine	360 mg	–	–
Citrus bioflavonoids	240 mg	–	–
Inositol	180 mg	–	–
Glutamine	180 mg	–	–
Methionine	60 mg	–	–
Grape seed	45 mg	–	–
Ginkgo biloba	36 mg	–	–
Germanium sesquioxide	20.7 mg	–	–
Boron	2400 μg	–	–
Vanadium	1194 μg	–	–
Nickel	29.4 μg	–	–

[a] Reference values are given as adequate intake as RDA not available.
[b] RDA varies with age.