Findings that shed new light on the possible pathogenesis of a disease
or an adverse effect

Efficacy and cost of micronutrient treatment of childhood psychosis

Megan Rodway,^{1,2} Annette Vance,² Amany Watters,² Helen Lee,³ Elske Bos,⁴ Bonnie J Kaplan⁵

¹Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada

²Mood and Anxiety Disorders Clinic, Calgary, Alberta, Canada

³Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

⁴Center for Integrative Psychiatry, Groningen, The Netherlands

⁵Department of Paediatrics, University of Calgary, Calgary, Alberta, Canada

Correspondence to Professor Bonnie J Kaplan, bonnie.kaplan@albertahealthservices.ca

Summary

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

BACKGROUND

Conventional treatment of hallucinations and delusions usually involves antipsychotic medications. Particularly in children, these substances have been associated with significant adverse events in the short-term (drowsiness, rigidity, constipation, weight gain, etc) as well as long-term increased risk for serious health consequences (diabetes, cardiovascular changes, etc).¹ The possibility of using nutrients instead of medication in childhood psychosis has been supported with one case report of a child with an extensive 6-year history of unsuccessful treatment with conventional pharmaceuticals,² after which symptom remission occurred with a complex nutrient formula. Though lacking numerical data, this report suggested that further exploration of this application was worthwhile, particularly as the nutrient formula is associated with few adverse events,³ and also appears to be generally safe.⁴

Traditional scientific methodology requires the manipulation of only one independent variable at a time, but treatment research with nutrients has begun to make much progress by employing complex independent variables, typically formulas containing balanced amounts of micronutrients (generally defined as vitamins, minerals, amino acids and essential fatty acids).

The broad-spectrum approach is an example of biomimicry, emulating nature to solve human problems, as the usual way in which we ingest nutrients is in balanced combinations provided naturally by foods. In physical health, the study of complex formulas has a long track record, showing improved immune function,⁵ increased resistance to communicable diseases,⁶ decreased

readmission to hospital⁷ and prevention of hip fractures.⁸ In the realm of mental function, complex formulas have been shown to benefit patients with dementia,^{9 10} to decrease aggression in schoolchildren,¹¹ and to decrease the levels of violence in incarcerated populations.^{12 13} Each of these studies has employed a unique combination of 3–20 ingredients, with the exception of the work on dementia, where a six-ingredient formula has been evaluated more than once in samples of geriatric patients.^{9 10}

We are aware of only one complex micronutrient formula for which extensive replication exists from multiple independent research teams, and the research happens to be focused on mental health. The 36-ingredient formula is called EMPowerplus (EMP+)¹ and consists of primarily vitamins, minerals, amino acids and antioxidants. There are currently 17 mental health publications on EMP+, involving replications by scientists at several academic institutions plus clinicians in private practice. Using many designs (within-subject case studies, case-control studies, open-label case series, case reports with extensive historical treatment information and large database analyses), the researchers have reported benefit in three countries for the treatment of mood and anxiety symptoms in children and adults.^{2 3 14–28} A compilation of safety and tolerability data from eight different research projects has also been

¹The ingredients of this formula are listed on the developer's website (Truehope.com): they consist of 14 vitamins, 16 minerals, 3 amino acids and 3 antioxidants. A typical therapeutic dose for significant mental disturbance is 15 capsules/day. No author of this or any other publication on this formula is financially affiliated with the company.

published.⁴ As the formula with the largest amount of published and ongoing research, and which is being used primarily in mental health, there is special interest in all facets of therapeutic use of EMP+. The case presented here is the first to provide a cost analysis of this treatment, only the second to show benefit for symptoms of psychosis,² and most importantly the first to provide empirical data documenting symptom response in the case of psychosis. As with a number of the other reports on the same formula,^{2 22 24} the child in this current report has been followed for a lengthy period of time, beyond the point at which expectancy effects would likely be influential.

The importance of this research is relevant not only because of the potential for treatment benefits to people with psychiatric symptoms, but even more so for understanding the possible pathogenesis of some forms of mental illness. Much has been written lately about the role of proinflammatory effects and impaired mitochondrial function in fostering neurological and mental impairments.^{29 30} Enhancement of micronutrient intake would be expected to augment mitochondrial function; as well, many nutrients are powerful antioxidants and exert anti-inflammatory effects.

CASE PRESENTATION

'Andrew' is the middle of three sons, the other two of whom apparently function normally both cognitively and emotionally. At age 8, Andrew was thoroughly investigated for a pervasive developmental disorder, which was ruled out. Instead, the diagnosis of anxiety disorder—NOS (not otherwise specified) was applied. By 10 years of age, he was feeling increasingly 'stressed' and 'overwhelmed'. He had initial and middle insomnia, restless sleep, fatigue, inattention, distractibility, difficulties completing school work and a growing inability to complete activities of daily living (such as eating and bathing). He vacillated between constant movement and standing motionless, with odd postures noted in his hands and head. He also engaged in self-injurious behaviour, such as punching his head with his closed fist or pulling at the hair on his arms. He had auditory hallucinations, including command hallucinations around harming himself. His thoughts were increasingly disorganised and he talked non-sensically to himself. He had frequent, intrusive and upsetting images of a violent and/or sexual nature, followed by ritualistic prayer and excessive apology. He refused food as he began to believe it was poisoned, and he lost weight.

INVESTIGATIONS

When he was an inpatient, initial investigations were all within normal limits: complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, creatinine, thyroid-stimulating hormone, electrolytes, liver function tests, fasting blood sugar, ammonia, lactate, Mg, Ca, lactate dehydrogenase, antinuclear antibodies, urine drug screen, amino acid analyses of urine and plasma, EEG, cranial CT and cranial MRI. One month later, a nasal (but not throat) swab was found to be positive for Strep A, his ASO titre was elevated (at 687, with 0–200 IU/ml being the normal range) and his anti-DNAse B titre went from 1:1360 to 1:960 over the course of the next 3 months (with normal limits for his age falling at 1:170).

DIFFERENTIAL DIAGNOSIS

At the time of his admission to hospital, he had a provisional diagnosis of psychosis—NOS/obsessive compulsive disorder (OCD)/borderline intellectual functioning. When he was an inpatient, pediatric autoimmune neuropsychiatric disorders associated with Strep was added to his list of diagnoses, along with generalised anxiety disorder (GAD) and social anxiety disorder.

TREATMENT

Conventional treatment

Andrew was admitted to the mental health inpatient service in a paediatric hospital from February to June/2008, with a provisional diagnosis of psychosis—NOS/OCD/borderline intellectual functioning. At that time, his score on the Children's Global Assessment Scale (CGAS) was 35. During his time as an inpatient, he could eat only small amounts and with persistent coaxing, because he had developed the delusion that the food had been poisoned. In addition, he frequently claimed that he was a murderer or an adulterer, and felt very guilty, which was associated with obsessive prayer. He was also unable to focus his attention on tasks such as reading. His walk was described as a shuffle, and he often exhibited tremors.

Andrew remained an inpatient for 6 months, receiving individual and family psychotherapy. Various medications were tried, alone and in combination, including quetiapine, risperidone, fluoxetine, fluvoxamine and clonazepam. Medication changes were due to intolerable side effects and/or inadequate treatment response. He was discharged in June 2008 on a regimen of risperidone (0.5 mg twice daily) and fluvoxamine (150 mg daily in divided doses). Although he had received some form of assessment and/or treatment from no fewer than four different child and adolescent psychiatrists over 6 months, plus consultation from a paediatric neurologist, there had been no apparent treatment benefit and his discharge CGAS score was still 35, identical to the score at admission.

Transition to micronutrients

The family decided to try micronutrient treatment on 20 September 2008, when Andrew was 11 years old, and they asked the outpatient mental health staff to continue their involvement with their son's mental health. The parents' decision was neither supported nor condemned by the follow-up outpatient team (MR, AV and AW), which continued to monitor his progress over the subsequent 14 months. The family was assisted in the treatment transition by the support staff at Truehope Nutritional Support Ltd (the formula's developer), who directed them in a cross-taper, gradually increasing his EMP+ while decreasing his psychiatric medications. Truehope staff members routinely ask clients to monitor symptoms so that treatment/dosage can be modified appropriately. For Andrew, anxiety, OCD and symptoms of psychosis were systematically monitored by home (daily) and school (usually weekly) with a list of symptoms approximating standard diagnostic criteria, but modified for this child's symptom expression (table 1). Each symptom was scored from 0 (not at all) to 3 (very much).

Table 1 Symptoms monitored

Anxiety-panic symptoms	Symptoms of obsessive compulsive disorder	Symptoms of psychosis
Shaking or trembling	Has recurrent or persistent and unwelcome thoughts or images	Hallucinations or delusions
Experiencing terror or fear of dying	Has worries that are excessive/beyond real life concerns	Extremely disorganised thoughts
A feeling of being out of control	Attempts to ignore, suppress or neutralise the above symptoms with some other thought or action	Inappropriate emotional response
Sweating	Suffers anxiety/feelings of distress	Abandonment of personal hygiene
Avoidance of normal activities because of a panic attack	Repetitive behaviours: sorting	Social withdrawal
Intense concern in a relatively relaxed situation	Repetitive behaviours: hand washing	Intense depression
Irritability	Repetitive behaviours: checking	Inability to concentrate
Lack of concentration, feeling of unreality or 'brain fog'	Repetitive behaviours: praying	Avoiding activities or hobbies
Shortness of breath, or a feeling of smothering, choking, tingling or numbness	Repetitive behaviours: counting	Thoughts of death or suicide
Heart racing or pounding, and or chest pains	Extreme religiousness or occupation with the occult	Forgetfulness
Inability to relax, trouble falling asleep		Unusual sensitivity to stimuli
Lightheadedness or dizziness		Rigid stubbornness
Excessive worry		Hyperactivity or inactivity
Frequent bathroom visits, and or nausea or stomach problems		

OUTCOME AND FOLLOW-UP

During the cross-taper, medications were reduced gradually, one-eighth at a time. After 1 month, he was medication free and taking 15–20 capsules of EMP+ per day (divided into three doses). His parents reported some difficult withdrawal symptoms (irritability and anger) until mid-December. Throughout the 4-week cross-taper, Andrew remained agitated, with, if anything, an increase in some self-injurious behaviours. However, between the fourth and sixth week of EMP+, which included the addition of 6–12 capsules of a solution of free amino acids that is used by the Truehope support staff to minimise withdrawal symptoms for individuals reducing psychiatric medications, both home and school noticed amelioration of obsessions and compulsions. For example, he no longer believed that his food was poisoned or that he was a 'bad' person. He ate a wider range of foods and in a shorter amount of time. He became more engaged with others (making some eye contact, initiating short conversations, asking developmentally appropriate questions and even smiling/laughing). His independence was also increasing (eg, initiating assignments on his own at school, without 1:1 assistance). The use of amino acids on an *ad lib* basis is well-supported by several decades of research demonstrating that multiple amino acids can reduce agitation and withdrawal symptoms in people struggling with drug dependence or addiction (see Chen *et al*³¹ for a review). There is no evidence, however, either in this child or in the scientific literature, that amino acids alone ameliorate symptoms of mood disorders or psychosis. The child described in this case continues to take a few *ad lib*; however, he takes EMP+ on a regular, daily basis.

Andrew's anxiety-related symptoms slowly abated over the course of the next 6–8 months, during which time he experienced more restorative sleep, less fatigue, improved concentration and diminished restlessness. His symptoms of psychosis also resolved after initiation of EMP+. He had four sessions of cognitive behaviour therapy during this time, consisting of gradual exposure/response prevention to help reduce a few rituals, cognitive restructuring to address unrealistic thinking, and breathing and visualisation exercises to promote self-calming. By 14 months, all diagnoses (except for borderline intellectual functioning and moderate-to-severe mixed receptive/expressive

language disorder) had fully remitted. He was discharged from the outpatient clinic with a CGAS of 70.

At the final outpatient case conference in June 2009, Andrew's parents spontaneously reported that he was better psychologically than he had been as a small child, even before coming to the attention of mental health services. For instance, he did not need as much reassurance around his safety and self-worth. The parents also reported cessation of all hallucinations, delusions (eg, food being poisoned), breath holding, excessive religiosity and tremors. Improvements were reported in his ability to concentrate (reading and doing his school work), socialisation, humour (joking with his brothers) and self-esteem. He has not needed any further mental health treatment for over 3 years.

Changes in symptom scores

Changes over time for the three symptom cluster scores were examined: Anxiety-panic, OCD and psychosis (figures 1–3). The anxiety and OCD symptoms were recorded for the entire 430-day study period. The family did not monitor the psychosis symptoms for the first 114 days, and the missing values were not replaced. All three symptom clusters had 14 days of missing data (3.3%) scattered over the study period, which were replaced by means of linear interpolation.

Figure 1 Symptoms of anxiety/panic.

Figure 2 Symptoms of obsessive compulsive disorder.

Regular ordinary least squares regression analysis assumes error terms to be independent. To account for the fact that data points taken over time tend to be correlated, time-series regression analyses were used to examine symptom changes.³² When residual autocorrelation is not accounted for, F and t tests can be seriously biased. In time-series regression, the series are adjusted for autocorrelation by fitting autoregressive-moving average (ARMA) models to the residuals.

The regression models included time as the independent variable to assess the rate of change. Time was centred at the first observation. Residual autocorrelation was detected using (partial) autocorrelation functions (ACFs and PACFs). ARMA parameters were estimated and included in each regression model. The residuals of the final models examined using ACFs and Ljung-Box tests to ensure they represented 'white noise'.³³ Series that showed heteroskedasticity were stabilised by using the natural log of the scores. Model selection was based on the normalised Bayesian Information Criterion (nBIC). Models were implemented using the SPSS V.17 Forecasting module. The significance level was 0.05.

Symptoms in all three clusters decreased over time. Table 2 shows the results for the final models of the time series analyses. All three models were fitted on the natural logs of the values, as all series showed heteroskedasticity. In all three regression models, the parameter for the linear trend ('Time') was highly significant ($p < 0.001$). The models explain up to 86% of the variance in the symptom scores. The regression coefficient for the linear decrease in anxiety symptoms and the one for OCD symptoms in the log-transformed models were about equal (coefficient

Figure 3 Symptoms of psychosis.

Table 2 Results of time-series regression models

Symptom cluster (log-transformed scores)	Model	Estimate	p Value	Model R ²
Anxiety-panic	Intercept	2.403	0.000	0.728
	Time	-0.0037	0.000	
	AR(lag 1)	0.445	0.000	
	AR(lag 2)	0.146	0.003	
Obsessive compulsive disorder	Intercept	2.716	0.000	0.848
	Time	-0.0041	0.000	
	AR(lag 1)	0.515	0.000	
	AR(lag 2)	0.348	0.000	
	MA(lag 2)	0.226	0.001	
Symptoms of psychosis	Intercept	2.594	0.000	0.861
	Time	-0.0068	0.000	
	AR(lag 1)	0.475	0.000	
	AR(lag 2)	0.172	0.001	

for anxiety=-0.0037; for OCD=-0.0041), suggesting that OCD symptoms decreased at a slightly higher rate than anxiety symptoms. This, however, may be a reflection of the fact that the child began with more OCD than anxiety symptoms. The linear trend for the logs of the psychosis symptoms was -0.0068, suggesting they declined at the highest rate. This, however, can probably be explained by the fact that psychosis symptoms were recorded for a shorter period of time.

A secondary question was whether changes in the different variables were related to each other and, if so, what the time lag for this relationship was. Cross-correlation functions (CCFs) for the different combinations of the symptom clusters were calculated for the double-prewhitened series of the log-transformed data, providing correlations adjusted for internal dependences. CCFs show contemporaneous correlations (lag 0) and lagged correlations between changes in pairs of variables, thus revealing the temporal order of the relationship. Prewhitening removes trends and serial dependency from the individual series so that the relationships can be examined without these influences, thus preventing spurious correlations.³⁴ Double prewhitening means that each of the two series is prewhitened.³⁵ The prewhitening process is necessary as CCFs of unprewhitened series tend to produce spurious correlations. The CCFs revealed significant correlations at lag 0 for all pairs of variables, and none of the lagged correlations reached significance. Thus, the relationships between the changes in the symptom scores were mainly concurrent. The contemporaneous correlations were quite large, especially between changes in anxiety and OCD symptoms ($r = 0.629$), as well as between changes in anxiety and psychosis symptoms ($r = 0.502$). The correlation between changes in OCD and psychosis symptoms

Figure 4 The child's self-reported hallucinations.

was somewhat smaller ($r=0.334$). Thus, changes in the different symptom clusters seem to co-vary over time, but temporal primacy of one variable over the others could not be established.

Initially, Andrew was unable to self-assess his visual and auditory hallucinations, but after being on EMP+ for about 2 months he spontaneously offered to do so. He scored each on a scale of 1–10 for 6 months beginning in January 2009 (see figure 4). A decreasing trend was observed also for these symptoms. School staff members also provided some records of symptom severity. Staff changes and school holidays are normal threats to the reliability of such measures, but in general they were confirmatory of the more consistent home-based reports.

Psychological assessments

Various assessments were available for Andrew from 2005 to 2009, but only two (WISC-IV and Adaptive Behavior Assessment System 2nd Edition (ABAS-II)) were administered both preintervention and postintervention (table 3). His IQ on the WISC-IV did not change: it remained in the fifth percentile. Andrew functions in the borderline range of cognitive ability with a moderate to severe expressive and receptive language impairment. There were some improvements on the ABAS-II, primarily at school, most notably in social behaviour and general adaptive functioning.

Cost analysis

With the parents' permission, a health economist (HL) requested Andrew's healthcare costs from the local health authority. All costs are presented in 2008 Canadian dollars. Data accessibility did not permit the capture of all costs: many physician costs for both inpatient admissions and outpatient services were not available. From 1 April 2008 to 19 September 2008 (pre-EMP+ period), his total healthcare cost \$158 829.53, excluding most physician fees (table 4). From 20 September 2008 to 31 March 2009,

Table 3 Performance on intelligence scales and a measure of adaptive behaviour, before and after micronutrient treatment

	February 2005 (premicronutrients)	July 2009	January 2010
WISC-IV	Full scale=5%ile VC=5%ile PR=10%ile WM=13%ile PS=13%ile	Full scale=5%ile VC=4%ile PR=23%ile WM=6%ile PS=13%ile	
ABAS-II	Parent report GAC=11%ile CC=21%ile SC=1%ile PC=25%ile Teacher report GAC=17%ile CC=23%ile SC=21%ile PC=23%ile		Parent report GAC=13%ile CC=7%ile SC=10%ile PC=32%ile Teacher report GAC=34%ile CC=32%ile SC=50%ile PC=32%ile

ABAS-II, Adaptive Behavior Assessment System, 2nd edition; CC, conceptual composite; GAC, general adaptive functioning; PC, practical composite; PR, perceptual reasoning; PS, processing speed; SC, social composite; WISC-IV, Wechsler Intelligence Scale for Children 4th edition; WM, working memory; VC, verbal comprehension.

Table 4 Costs of 6 months of conventional inpatient treatment compared to 6 months of outpatient follow-up with micronutrient treatment

Types of services	Frequency	Costs (in 2008 CDN \$)
A. Inpatient treatment		
Inpatient admission (75 days)	1	148792.64
Emergency visit	2	250.20
Mental health day treatments	51	5379.41
Social work	1	155.28
Ambulatory services	3	616.76
Neurophysiology lab	1	272.34
Mental health specialty clinics	13	3108.77
Speech-language pathology	1	254.14
Total		158829.53
B. Outpatient, nutrient treatment		
Mental health outpatient specialty clinics	4	910.09
Allied health outpatient clinical support	4	899.74
Approximate cost of micronutrients		1040
Total		2849.83

with the outpatient team monitoring the family as they transitioned to micronutrients, providing support and some sessions in cognitive behaviour therapy, the costs were \$2 849.83, of which \$1 040 was the actual cost of the micronutrients. In other words, 6 months of professional inpatient time which did not result in symptom improvement cost approximately 150 times the cost of micronutrient treatment.

Safety and tolerability

Results from blood tests were followed for about 2 years and remained within normal limits. No adverse events have been noted.

Extended follow-up information

After 4 years on EMP+, Andrew continues to take 15–20 capsules a day plus some amino acids. The current cost of his treatment is about \$150/month, which the parents must pay themselves as natural health products are not covered by any insurance. He has no symptoms of psychosis.

DISCUSSION

Most of the reports using EMP+ have focused on mood and anxiety symptoms, but in one article, its efficacy was documented for a young boy who experienced some symptoms of psychosis.² That child was initially diagnosed with bipolar disorder–NOS, then later with bipolar disorder–I with psychotic features, as well as GAD, and OCD. From 6–12 years, he exhibited symptoms of anxiety, obsessions, self-injurious behaviour and mood instability, plus auditory hallucinations at least 100 times per week, consisting of voices instructing him to carry out obsession-related acts. Extensive documentation of the boy's treatment with conventional pharmaceuticals from the ages of 6–12 was also reported: medications from 2001 to 2008 included lithium, risperidone, clonidine, trazodone, gabapentin, divalproex, aripiprazole, lorazepam, lamotrigine, among others. The authors reported that no combination of medications ever resulted in

consistent improvement. In January 2008 the family transitioned him from medications to EMP+ over the course of 19 days, at which point his behaviour normalised and all diagnoses remitted. At 14 months follow-up, he continued to enjoy good mental health, taking a daily therapeutic dose of EMP+, sometimes supplemented with an amino acid solution (whey protein).

Psychosis is difficult to treat and unlikely to remit on its own. Important predictors of the maintenance of minimally symptomatic status are being young and having low baseline symptom severity.³⁶ In the current report the child was young, but symptom severity was very high. After 6 months in which intensive inpatient treatment resulted in no improvement, the family transitioned him from medication to a complex micronutrient formula. The child was off all psychotropic medications in about 4 weeks, and taking only micronutrients. These results are consistent with the report by Frazier *et al*² in which complete symptom remission followed 19 days of transition to EMP+ in a child whose illness had been very severe for the previous 6 years. In that case study, however, in spite of the richness of the clinical history, there were no quantitative data to demonstrate the symptom improvement.

Although the literature on micronutrients for the treatment of unstable mood is rather extensive,³⁷ there is much less published information on OCD or symptoms of psychosis. One child with atypical OCD (obsessions, but no compulsions) was reported in 2002²⁴: treated in a within-subject crossover design with an earlier version of EMP+, his obsessions completely remitted while taking the formula, returned when the formula was removed, and remitted again when treatment was reinstated. In a young man studied in another within-subject crossover design with the current version of EMP+, Rucklidge²¹ demonstrated on-off control of the intense OCD symptoms. This case was particularly interesting for other reasons: there was a 1-year history of historical data recorded from prior treatment with cognitive behavioural therapy, the youth himself had no positive expectation of benefit from EMP+, and each treatment reversal was associated with psychological assessments confirming improvements in depression, anxiety and OCD.

There are other promising nutrient interventions for psychosis, such as *N*-acetyl cysteine,³⁸ but the single-nutrient therapies tend to be adjuncts. Broad-spectrum micronutrient treatments such as the one described here are primary treatments, and possibly not safe to use in a supplementary manner because micronutrients can amplify the effect of psychiatric medications.^{28 39 40}

There are a number of limitations inherent in a case study of this type. Andrew's treatment was not designed *a priori* as research, so assessments were not blinded, and pre-post measures of cognitive and mental function were limited. Most of the data were dependent on parent report, although confirmatory information was provided from school reports, Andrew's self-reported score for hallucinations, and observations from the outpatient mental health team.

One interesting question is whether there were any clues that nutrition might be relevant for this particular child. We offer as a speculative comment the idea that

breath-holding may have been such a clue. His parents reported that breath-holding was a frequent occurrence for Andrew from birth, especially in moments of fatigue, stress, or illness. As recently shown in a Cochrane review,⁴¹ iron supplementation effectively treats this problem. Whether Andrew has some broader metabolic dysfunctions affecting micronutrient needs is not known at this time.

Learning points

- Broad-spectrum formulas of vitamins and minerals (micronutrients) are showing benefit for the treatment of both physical and mental symptoms.
- One case study has previously reported the efficacy of this treatment in a child with severe psychosis; the current case found similar results, supported by quantitative measures.
- Psychosis is difficult to treat, and conventional treatments often have adverse long-term health effects; these facts lend impetus to the importance of carrying out further research with broad spectrum nutrient formulas.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. McIntyre RS, Jerrell JM. Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. *Arch Pediatr Adolesc Med* 2008;**162**:929–35.
2. Frazier EA, Fristad MA, Arnold LE. Multinutrient supplement as treatment: literature review and case report of a 12-year-old boy with bipolar disorder. *J Child Adolesc Psychopharmacol* 2009;**19**:453–60.
3. Mehl-Madrona L, Leung B, Kennedy C, *et al*. Micronutrients versus standard medication management in autism: a naturalistic case-control study. *J Child Adolesc Psychopharmacol* 2010;**20**:95–103.
4. Simpson JSA, Crawford SG, Goldstein ET, *et al*. Safety and tolerability of a complex micronutrient formula used in mental health: a compilation of eight datasets. *BMC Psychiatry* 2011;**11**:62.
5. Mitchell BL, Ulrich CM, McTiernan A. Supplementation with vitamins or minerals and immune function: can the elderly benefit? *Nutr Res* 2003;**23**:1117–39.
6. Barringer T, Kirk J, Santaniello A, *et al*. Effect of a multivitamin and mineral supplement on infection and quality of life: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003;**138**:365–71.
7. Gariballa S, Forster S, Walters S, *et al*. A randomized, double-blind, placebo-controlled trial of nutritional supplementation during acute illness. *Am J Med* 2006;**119**:693–9.
8. Sato Y, Honda Y, Iwamoto J, *et al*. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA* 2005;**293**:1082–8.
9. Remington R, Chan A, Paskavitz J, *et al*. Efficacy of a vitamin/nutriceutical formulation for moderate-stage to later-stage Alzheimer's disease: a placebo-controlled pilot study. *Am J Alzheimers Dis Other Dement* 2009;**24**:27–33.
10. Chan A, Paskavitz J, Remington R, *et al*. Efficacy of a vitamin/nutriceutical formulation for early-stage Alzheimer's disease: a 1-year, open-label pilot study with a 16-month caregiver extension. *Am J Alzheimers Dis Other Dement* 2009;**23**:571–85.
11. Schoenthaler SJ, Bier ID. The effect of vitamin-mineral supplementation on juvenile delinquency among American schoolchildren: a randomized, double-blind placebo-controlled trial. *J Altern Complement Med* 2000;**6**:7–17.
12. Gesch CB, Hammon SM, Hampson SE, *et al*. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. *Br J Psychiatry* 2002;**181**:22–8.

13. **Zaalberg A**, Nijman H, Bulten E, *et al*. Effects of nutritional supplements on aggression, rule-breaking, and psychopathology among young adult prisoners. *Aggressive Behav* 2010;**36**:117–26.
14. **Rucklidge JJ**, Andridge R, Gorman B, *et al*. Shaken but unstirred? Effects of micronutrients on stress and trauma after an earthquake: RCT evidence comparing formulas and doses. *Hum Psychopharmacol* 2012;**27**:440–54.
15. **Rucklidge JJ**, Blampied NM. Post-earthquake psychological functioning in adults with attention-deficit/hyperactivity disorder: positive effects of micronutrients on resilience. *N Z J Psychol* 2011;**40**:51–7.
16. **Rucklidge JJ**, Johnstone J, Harrison R, *et al*. Micronutrients reduce stress and anxiety following a 7.1 earthquake in adults with attention-deficit/hyperactivity disorder. *Psychiatry Res* 2011;**189**:281–7.
17. **Rucklidge J**, Taylor M, Whitehead K. Effect of micronutrients on behavior and mood in adults with ADHD: evidence from an 8-week open label trial with natural extension. *J Atten Disord* 2011;**15**:79–91.
18. **Rucklidge JJ**, Harrison R, Johnstone J. Can micronutrients improve neurocognitive functioning in adults with ADHD and severe mood dysregulation? A pilot study. *J Altern Complement Med* 2011;**17**:1125–31.
19. **Rucklidge JJ**, Gately D, Kaplan BJ. Database analysis of children and adolescents with bipolar disorder consuming a micronutrient formula. *BMC Psychiatry* 2010;**10**:74.
20. **Rucklidge JJ**, Harrison R. Successful treatment of bipolar disorder II and ADHD with a micronutrient formula: a case study. *CNS Spectr* 2010;**15**:289–95.
21. **Rucklidge JJ**. Successful treatment of OCD with a micronutrient formula following partial response to Cognitive Behavioral Therapy (CBT): a case study. *J Anxiety Disord* 2009;**23**:836–40.
22. **Gately D**, Kaplan BJ. Database analysis of adults with bipolar disorder consuming a micronutrient formula. *Clin Med Insights Psychiatry* 2009;**4**:3–16.
23. **Kaplan BJ**, Fisher JE, Crawford SG, *et al*. Improved mood and behavior during treatment with a mineral-vitamin supplement: an open-label case series of children. *J Child Adolesc Psychopharmacol* 2004;**14**:115–22.
24. **Kaplan BJ**, Crawford SG, Gardner B, *et al*. Treatment of mood lability and explosive rage with minerals and vitamins: two case studies in children. *J Child Adolesc Psychopharmacol* 2002;**12**:205–19.
25. **Kaplan BJ**, Simpson JS, Ferre RC, *et al*. Effective mood stabilization with a chelated mineral supplement: an open-label trial in bipolar disorder. *J Clin Psychiatry* 2001;**62**:936–44.
26. **Frazier EA**, Fristad MA, Arnold LE. Feasibility of a nutritional supplement as treatment for pediatric bipolar spectrum disorders. *J Altern Complement Med* 2012;**18**:678–85.
27. **Simmons M**. Nutritional approach to bipolar disorder. *J Clin Psychiatry* 2003;**64**:338; author reply 338–9.
28. **Popper CW**. Do vitamins or minerals (apart from lithium) have mood-stabilizing effects? *J Clin Psychiatry* 2001;**62**:933–5.
29. **Leonard B**, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci Biobehav Rev* 2012;**36**:764–85.
30. **Gardner A**, Boles RG. Is a 'mitochondrial psychiatry' in the future? A review. *Curr Psychiat Rev* 2005;**1**:255–71.
31. **Chen TJ**, Blum K, Chen AL, *et al*. Neurogenetics and clinical evidence for the putative activation of the brain reward circuitry by a neuroadaptagen: proposing an addiction candidate gene panel map. *J Psychoactive Drugs* 2011;**43**:108–27.
32. **Ostrom CW**. *Time series analyses: regression techniques*. London: Sage University Papers, 1990.
33. **Ljung GM**, Box GEP. On a measure of lack of fit in time series models. *Biometrika* 1978;**65**:297–303.
34. **Chatfield C**. *The analysis of time series: an introduction*. 6th edn. London: Chapman & Hall/CRC Texts in Statistical Science, 2004.
35. **Brockwell PJ**, Davis RA. *Time series: theory and methods*. 2nd edn. New York, NY: Springer Series in Statistics, 2006.
36. **Treuer T**, Martenyi F, Saylan M, *et al*. Factors associated with achieving minimally symptomatic status by patients with schizophrenia: results from the 3-year intercontinental schizophrenia outpatients health outcomes study. *Int J Clin Pract* 2010;**64**:697–706.
37. **Kaplan BJ**, Crawford SG, Field CJ, *et al*. Vitamins, minerals, and mood. *Psychol Bull* 2007;**133**:747–60.
38. **Berk M**, Copolov D, Dean O, *et al*. N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. *Biol Psychiatry* 2008;**64**:361–8.
39. Herbal and dietary supplements for depression. *Harv Ment Health Lett* 2008;**25**:4–5.
40. **Stahl SM**. Novel therapeutics for depression: L-methylfolate as a trimonoamine modulator and antidepressant-augmenting agent. *CNS Spectr* 2007;**12**:739–44.
41. **Zehetner AA**, Orr N, Buckmaster A, *et al*. Iron supplementation for breath-holding attacks in children. *Cochrane Database Syst Rev* 2010;**5**: CD008132.

Copyright 2012 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Rodway M, Vance A, Watters A, Lee H, Bos E, Kaplan BJ. Efficacy and cost of micronutrient treatment of childhood psychosis.

BMJ Case Reports 2012;10.1136/bcr-2012-007213, Published XXX

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow