Effective Mood Stabilization With a Chelated Mineral Supplement: An Open-Label Trial in Bipolar Disorder

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

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

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

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

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See also Commentary on page 933.

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Solid scientific research shows that many dietary nutrients, including minerals and vitamins, are essential for normal brain function. For instance, deficient levels of various B vitamins are related to pathologic brain and behavior disorders ranging from Korsakoff's syndrome to pellagra. Recent work on folic acid (vitamin B_9) suggests that low levels may be associated with depressive symptomatology and poor response to antidepressant medication.[1,2]

Less is known about the role of trace elements, but there is considerable evidence that these too may be essential for normal brain function. Zinc provides a good example. Most of the excitatory neurons of the cerebral cortex have glutamate as their primary transmitter. One type of glutaminergic neuron accumulates zinc within vesicles at axon terminals and releases it into the synapse upon firing.[3] The precise roles of zinc in synaptic function are not known, although its presence is certain,[4] and there are zinc-binding sites on one subset of glutamate receptor called the NMDA (*N*-methyl-D-aspartate) receptor.[5] Zinc, copper, and magnesium all appear to play important modulatory roles in controlling the NMDA receptor,[6–8] which has been implicated in various forms of cortical plasticity, including learning.[9] It is possible, then, that decreased levels of some minerals in the brain may produce abnormal NMDA-mediated plasticity and subsequent abnormalities in behav-

ior. Other trace elements such as magnesium and copper[6,10] are also thought to have receptor sites in the cortex and might also presumably affect normal cortical functioning.

Recent studies have shown low plasma levels of zinc and other minerals in people with mood and behavior disorders. Maes and colleagues[11,12] found lower serum zinc levels in 48 unipolar depressed patients in comparison to 32 volunteers with normal mental health. Walsh and colleagues[13] evaluated the copper and zinc levels in 135 assaultive, incarcerated males in comparison to controls. They found an inverse relationship between zinc and the seriousness of the behavior, ranging from verbal assault to aggravated and violent assault: the lower the zinc, the greater the rate of violent behavior.

Toren and colleagues[14] reported lower serum zinc levels in 43 children with attention-deficit/hyperactivity disorder (ADHD) than in comparable controls. A study of 18 boys with ADHD who underwent a placebo-controlled trial of amphetamine treatment found that higher baseline hair zinc levels predicted a better behavioral response to the stimulant medication.[15] Subsequent analyses of the same data, but employing a more thorough determination of zinc levels from 3 measures (hair, red cell, and urine), confirmed the initial finding: those children with adequate zinc were better stimulant responders than those with borderline zinc levels or those who were zinc-deficient.[16]

Studies of other minerals have yielded some interesting findings. Calcium imbalance caused by hyperparathyroidism has long been known to affect anxiety, depression, and cognitive function,[17,18] and in fact, calcium balance in general has been shown to play an important role in mood disorders.[19] A recent study reported significantly decreased bone mineral density in 24 women with current major depressive disorders or with a past history of depression,[20] and women with osteoporosis exhibited elevated depression scores on a symptom inventory.[21] Significant iron deficiency results in mental and behavioral symptoms such as irritability, aggression, or mental retardation.[22,23] Because iron-deficient rats have low dopamine D_2 receptor levels,[24] Weiser and colleagues[25] looked at 26 medication-free schizophrenics in comparison to controls and found significantly low serum iron. Others have reported that both the cerebrospinal fluid and serum of people with schizophrenia were low in magnesium.[26]

The evidence supporting the importance of minerals and vitamins in central nervous system functioning provided some scientific support for our interest in studying a supplement that is gaining considerable clinical attention in Canada and in many areas of the United States. This supplement was developed over several years by some families in Alberta and eventually was manufactured and distributed from Utah.* It consists of 36 ingredients, primarily chelated minerals. The formulation was based in part on agricultural knowledge of the treatment of stress and mood problems in cattle and hogs: transport and handling of livestock have been shown to have a particularly large impact on chloride, potassium, calcium, and magnesium, thus altering normal electrolyte balance and overall health.[27] Described herein are the data collected in open trials of the first, consecutive, and unselected 11 cases of bipolar disorder in adults evaluated while taking this supplement and followed for at least 6 months, testing the hypothesis that a broad-based nutritional supplement that emphasizes trace minerals would help stabilize mood.

METHOD

The Conjoint Health Research Ethics Board of the University of Calgary, Calgary, Alberta, Canada, approved the protocol for an open case series in adults with bipolar disorder, using the dietary supplement E.M.Power+. The experimental nature of the work was carefully described to each patient, who then signed a consent form.

The overall sample for this open-label case series consisted of 14 adults (10 men and 4 women). The 3 patients who dropped out were female, aged 24, 35, and 45 years. The dropout patients took the supplement for at least 3 weeks (range, 3–10 weeks). The sample of completers consisted of 10 men and 1 woman, aged 19 to 46 years (mean ± SD = 29.4 ± 10.7 years). Six cases fulfilled DSM-IV criteria for bipolar I, 4 fulfilled criteria for bipolar II, and 1 fulfilled criteria for bipolar disorder not otherwise specified (NOS). Patients' psychiatrists confirmed their clinical diagnoses using the Structured Clinical Interview for DSM-IV Axis I Disorders (the SCID-I).[28] The time since diagnosis for each patient is listed in Table 1, along with their medication histories.

Patients were excluded if they were pregnant, trying to get pregnant, or lactating; if they had untreated or unstable thyroid disease; if they had received ECT within the previous 6 months; if their psychotropic medications had been altered within the previous 4 weeks; if they were currently taking antibiotics (which may disrupt intestinal absorption of nutrients); if they had any abnormality of metabolism (renal disease, hemachromatosis, hyperlipidemia, etc.); if there was evidence of substance abuse in the previous 6 months; if they suffered from dementia, mental retardation, or any neurologic disorder affecting language or comprehension; if they suffered from any other unstable medical condition; or if they had begun any other new treatment recently such as cognitive psychotherapy. Patients were not excluded for comorbid diagnoses: 1 patient had obsessive-compulsive disorder, 1 had dysthymic disorder, and 1 had ADHD. Participants were

*After several years of development by the Synergy Group of Canada/Truehope Institute, in April 2000, the formulation of the supplement was finalized and named E.M.Power+ ("essential mineral" power). A list of ingredients for 1/4 the full adult dose can be found in the Appendix.

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Table 1. Characteristics of 14 Patients With Bipolar Disorder

Patient	Age (y), Gender, Diagnosis	Years Since Diagnosis	Past Medications	ECT?/Hospitalizations?
1	21, M, bipolar I	2	Benztropine, bupropion, buspirone, clonazepam, chlorpromazine, dextroamphetamine, diazepam, fluoxetine, imipramine, lithium, methylphenidate, nortriptyline, paroxetine, risperidone, sertraline, trazodone, valproic acid, zolpidem	No/No
2	19, M, bipolar I	3	Carbamazepine, clomipramine, clonazepam, desipramine, fluoxetine, fluvoxamine, haloperidol, imipramine, lamotrigine, lithium, nortriptyline, paroxetine, quetiapine, risperidone, sertraline, thioridazine, valproic acid	Yes/Yes
3	23, M, bipolar NOS	4	Bupropion, dextroamphetamine, fluoxetine, pemoline, sertraline, venlafaxine	No/No
4	20, M, bipolar I	3	Desipramine, fluoxetine, imipramine, lithium, methylphenidate, paroxetine, sertraline, valproic acid, venlafaxine	No/No
5	21, M, bipolar II	3	Clonazepam, fluoxetine, paroxetine, zolpidem	No/Yes
6	45, M, bipolar II	3	Bupropion, dextroamphetamine, fluoxetine, lithium, methylphenidate, thioridazine, trifluoperazine, valproic acid, venlafaxine	No/Yes
7	34, M, bipolar I	16	Alprazolam, clonazepam, desipramine, fluoxetine, lithium, risperidone, sertraline, trazodone, valproic acid, venlafaxine, zolpidem	No/No
8	46, M, bipolar I	7	Bupropion, clonazepam, clozapine, fluoxetine, gabapentin, lamotrigine, lithium, olanzapine, quetiapine, valproic acid	Yes/Yes
9	21, M, bipolar I	3	Paroxetine, valproic acid	No/Yes
10	31, M, bipolar II	2	Chlorpromazine, citalopram, dextroamphetamine, fluvoxamine, gabapentin, lamotrigine, levothyroxine, lithium, lorazepam, methotrimeprazine, nefazodone, olanzapine, sertraline, valproic acid, venlafaxine	No/Yes
11	42, F, bipolar II	19	Carbamazepine, lithium, sertraline, trifluoperazine	Yes/Yes
12	35, F, bipolar I	18	Clonazepam, lithium carbonate, lorazepam, olanzapine, paroxetine, risperidone, topiramate, valproic acid, zopiclone	No/Yes
13	45, F, bipolar I	20	Amitriptyline, citalopram, doxepin, fluoxetine, imipramine, lithium carbonate, lorazepam, methotrimeprazine, nefazodone, trazodone, trimipramine maleate, venlafaxine	Yes/Yes
14	24, F, bipolar II	5	Bupropion, carbamazepine, chlorpromazine, clonazepam, fluoxetine, lithium carbonate, nefazodone, paroxetine, risperidone, sertraline, valproic acid	No/Yes

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asked to stop all other nutritional supplementation at study entry.

The intervention consisted of the mineral and vitamin formulation in capsule form. The full dose requires the ingestion of 32 capsules per day because of the bulk of chelated minerals. Patients were started immediately on the full dose on the first treatment day and were allowed to distribute the capsules into 4 doses across the day.

Patients were assessed by their own psychiatrists at study entry and during the intervention with the following measures: the Hamilton Rating Scale for Depression (HAM-D),[29] the Young Mania Rating Scale (YMRS),[30] and the Brief Psychiatric Rating Scale (BPRS).[31] These 3 outcome measures were employed at study entry and at each visit, along with an Adverse Events Form used to monitor side effects. Patients were seen by their psychiatrists once a week for the first 4 weeks of the open trial. Appointments were decreased to a monthly schedule if a patient's score on the HAM-D decreased to less than 8 (a HAM-D score of about 14–17 is generally considered to indicate clinically important levels of depression)[32] or if the score on the BPRS decreased to less than 6 (a BPRS score of 14–20 is generally thought to indicate clinically meaningful levels of psychiatric symptomatology).[33,34] Patients attended at least 7 appointments with their psychiatrists during the intervention (range, 7–18 appointments).

Psychiatrists were permitted to manage their patients as usual, using their clinical judgment regarding care. This

Table 2. Medications Before and During Treatment With a Chelated Mineral Supplement

Patient	Medications at Study Entry	Time on Supplement (wk)	Current Medications
1	Clonazepam, lithium, nortriptyline, risperidone, zolpidem	40	Clonidine, lamotrigine, olanzapine, quetiapine
2	Carbamazepine, clonazepam, lamotrigine, propranolol quetiapine, sertraline	59	Lamotrigine
3	None	41	None
4	None	58	None
5	Paroxetine	28	None
6	Fluoxetine, lithium, methylphenidate, venlafaxine	86	Nortriptyline
7	Clonazepam, zolpidem	26	Zolpidem
8	Clonazepam, lamotrigine, lithium, quetiapine	34	Quetiapine
9	Paroxetine, valproic acid	45	None
10	Lithium, lorazepam, sertraline, valproic acid	40	Lithium
11	Carbamazepine, sertraline	26	Sertraline
12	Risperidone, topiramate	6	None
13	Clonazepam, moclobemide, valproic acid	10	Clonazepam, moclobemide
14	Citalopram, lorazepam, topiramate	3	Citalopram, lorazepam, quetiapine, topiramate

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included adjustment of concurrent psychiatric medications as they saw fit. They were, however, also given instructions based on the developers'/distributor's suggestions on managing expected supplement-medication interactions. The instruction was that medication reductions should be considered in the event of interactions.

Fourteen patients began the protocol and 11 completed a minimum of 6 months; as shown in Table 2, we were able to follow most for much longer (range, 6–21 months). The reasons that patients dropped out of the study (N = 3) were varied. In 1 case that was monitored by someone outside the research team, the psychiatrist violated the protocol and did not monitor the supplement-medication interactions as required. This patient took the supplement for 3 weeks and became very agitated and tearful. The psychiatrist admitted the patient to hospital and discontinued the supplement rather than altering medication. In the other 2 cases, definite symptom improvement was demonstrable on the daily and periodic data collection systems. Both patients became noncompliant, however, and were removed from the protocol because of refusing to follow their research psychiatrists' recommendations. In 1 of the cases, the patient took the supplement for 6 weeks as part of this study and was able to eliminate both of the medications that she was taking initially. This patient is continuing to take the supplement on her own (apparently with considerable success). She did, however, refuse to submit to a final assessment for this study, because of conflicts with psychiatrists on the research team.

Statistical Analysis

The outcome variables were analyzed using paired t tests to assess the difference between scores at study entry compared with scores at the last study visit. Two sets of analyses were conducted: intent-to-treat analysis (N = 14) and analysis of patients who completed the open trial (N = 11). 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

Ten patients had been hospitalized at least once, of whom 4 had prior electroconvulsive therapy (see Table 1). The mean number of psychotropic medications tried prior to study entry was 10 (range, 2–18), and mean years of prior treatment were 6.7 (range, 2–20).

Table 2 lists the psychotropic medications at entry into the trial, the number of weeks each patient has taken the supplements thus far, and the medications at the most recent visit. In some cases, the lack of medication at study entry is misleading. For instance, patient 4 had taken many medications for the 3 years prior to this study (as shown in Table 1). None had been effective, so a month prior to entering this study he had chosen to discontinue all psychotropic medications. At entry, the mean ± SD number of medications prescribed for this sample was 2.7 ± 1.8.

Symptom Reduction

Intent-to-treat analysis. A series of paired t tests with all 14 subjects revealed statistically significant decreases in scores over the course of the study on the HAM-D and YMRS (Table 3). There was also a trend for lower scores on the BPRS.

Analysis of completers. The same analyses were repeated on the 11 patients who completed the open trial.

Table 3. Outcome Measures at Study Entry and at Last Visit[a]

	Entry Visit		Last Visit		Full Sample			Restricted Sample[b]		
Outcome	Mean	SD	Mean	SD	Paired t	df	p	Paired t	df	p
Intent-to-treat (N = 14)										
HAM-D	17.8	8.1	9.2	9.0	2.64	12	< .05			
BPRS	30.8	30.1	10.2	11.0	2.02	11	< .10			
YMRS	15.9	11.9	6.0	6.4	3.73	11	< .01			
Completers only (N = 11)										
HAM-D	19.0	8.0	5.4	5.6	5.59	9	< .01	4.99	8	< .01
BPRS	35.3	31.2	7.4	8.6	2.57	9	< .05	2.34	8	< .05
YMRS	15.1	9.8	6.0	6.9	4.11	9	< .01	3.61	8	< .01

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.
[b]Restricted sample consists of 10 patients who completed the study, omitting patient 1.

Table 4. Change in Outcome Measures from Study Entry to Last Visit by Subject

	HAM-D		BPRS		YMRS	
Patient	Entry	Last	Entry	Last	Entry	Last
1[a]	28	14	40	15	27	16
2[a]	25	2	54	2	12	1
3[a]	18	2	38	2	22	3
4[a]	21	1	113	3	6	3
5	16	…	23	21	18	16
6[a]	17	3	29	2	15	0
7	11	6	10	22	25	15
8[a]	25	16	20	7	24	6
9	21	8	…	…	…	0
10[a]	23	0	25	0	2	0
11	1	2	1	0	0	0
12	9	15	12	34	38	9
13	24	28	20	…	2	…
14	8	22	5	14	2	3

[a]Patient is a responder (as indicated by ≥ 20% reduction on all 3 measures).

Paired t tests revealed significant decrements in scores from study entry to the most recent visit on all 3 outcome measures assessing depression (HAM-D), mania (YMRS), and general psychiatric status (BPRS) (see Table 3). The effect size was large for each of the 3 outcome measures (> .80). These patients have now been followed for a mean ± SD of 43.9 ± 18.0 weeks (range, 26–86 weeks).

The mean symptom reduction was 55% on the HAM-D, 60% on the BPRS, and 66% on the YMRS (Table 4). To evaluate the number of patients showing a clinically significant response to the supplement, we defined as a responder any patient who exhibited at least a 20% decrease on all 3 outcome measures. Two patients (patient 5 and patient 9) were excluded because of missing data, and 1 patient (patient 11) because she was asymptomatic at study entry, so that a 20% decrease was not possible. Of the remaining 8 patients, 7 met criteria for responder status (Table 4). The remaining patient (patient 7) met responder criteria for 2 of the 3 measures. Although his BPRS score actually increased considerably from 10 to 22, an examination of his interview data revealed that this was not due to the presence of any psychotic or manic symptoms. His symptoms were primarily guilt, anxiety, and tension, which his psychiatrist reports were due to a profound reaction to the discovery that his family had found out that he was significantly in debt from a gambling addiction.

Medication Reduction in Completers

The number of psychotropic medications was reduced by more than 50% in these patients after they began taking the supplement, from a mean of 2.7 ± 2.0 per patient at study entry to 1.0 ± 1.1 at the most recent visit (t = 3.54, df = 10, p < .01). The protocol allowed psychiatrists to change medications freely as part of their patient management. Two patients were medication-free at the start of the open trial and at their last visit: patient 3 was medication-free during the entire study period; patient 4 tried 2 medications during the open trial but was medication-free at the start of the study and again by the last study visit. All other patients were on different medication regimens at the start and finish. The medication regimen of 1 patient (patient 1) was especially different at the end of the trial compared with study entry, so that the patient's results were discarded and the data were reanalyzed. As shown in Table 3, the results from this restricted sample were similar to the overall results.

In 2 cases, the supplement has replaced psychoactive medications and the patients have remained well. In general, patients have reported feeling the first effect of the supplement within 2 weeks. Medications were decreased gradually as the supplement began to influence the patient's mood.

Side Effects

The only side effect reported was nausea, especially if patients forgot to take the supplement with food. In 2 cases the nausea was sustained over several days. Patient 9 chose to increase his food intake with his pills and briefly use antinausea medication to cope with the problem; the nausea of patient 10 was alleviated by dose reduction and a gradual increase up to full dose.

Despite the challenge of taking 32 pills daily, the patients reported that the supplement was easy to tolerate. Also, some patients reported being able to distinguish

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their subjective reactions to the supplement (which they described as feeling more normal) from the benefit they have derived from psychotropic medication treatment (described as symptom reduction or masking).

DISCUSSION

We have been exploring the possible clinical benefit of a broad-based nutritional supplement consisting of 36 items, primarily chelated minerals. The data reported here provide the first, preliminary scientific validation of the supplement's efficacy and suggest that further research is warranted.

Although much additional research is needed (to replicate these findings, to address the mechanism of action, etc.), our preliminary data and the general clinical experience of psychiatrists who are monitoring patients in our trials indicate that the supplement has a beneficial psychotropic effect and is not acting in only an adjunctive manner. Consequently, the largest challenge in dealing with the supplement is the interaction with psychiatric medications. The observation made by many patients and clinicians who have used this preparation is that the supplement interacts with psychiatric medications. The distributor recommends decreasing psychiatric medications in this situation, and despite significant concerns about safety, we have found that this seems to be a reasonable approach.

In this case series, the diagnoses of bipolar disorder in these 11 patients were made clinically by psychiatrists and confirmed by the SCID diagnostic interview. Patients were treated with the nutritional supplement on an open-label protocol and monitored systematically for a minimum of 6 months (range, 6–21 months). The changes in all 3 outcome measures were statistically and clinically significant. As a group, it was possible for the patients to be clinically managed on fewer psychotropic medications (more than a 50% reduction). Individually, also, all 11 patients benefited from the supplement. In the 1 patient who was asymptomatic at study entry (patient 11), whose benefit cannot be demonstrated as a symptom reduction, a decrease in number of medications was achieved without a significant elevation in symptoms.

There are weaknesses in this case series. First, purely by chance, 10 of these patients were men, thus hindering generalizations to women. Second, as in any case series, there is a weakness in not having a placebo control. We would point out that these patients had been exposed previously to many interventions, and their positive expectancy of benefit did not work with these prior efforts. Also, it would be surprising for a placebo effect to be sustained as long as 6 months. Nevertheless, a randomized, placebo-controlled trial has been funded and is currently underway. A third potential source of bias is from the psychiatrists themselves. As in any open-label study, unblinded assessments can result in exaggerated results. In this particular case, though, it would be fair to say that the majority of the psychiatrists expected to see no benefit from nutritional supplementation, so perhaps this form of bias was not a major influence on our data. The use of concurrent psychiatric medication was a fourth weakness in this case series: the changes in medications made by the psychiatrists as part of normal clinical care make it difficult to attribute symptom changes specifically to the nutritional supplement. Our current randomized trials are evaluating patients who are unmedicated.

It would be a mistake to assume that the breadth of the intervention was a weakness. At present, there is not enough knowledge available to hypothesize that one or several of the ingredients has any special effectiveness in treating bipolar disorder. The selection of a broad-based mineral and vitamin supplement was based on an approach of inclusiveness rather than premature focus or closure, as well as a strategy of attempting to maximize the chances that some clinical effect might be found. There have been many failed attempts to treat mental illness with a single ingredient or group of nutrients, and also possibly some limited successes.[35,36] Given the complexity of the mammalian central nervous system and homeostatic mechanisms, it is reasonable that a very broad approach to nutritional supplementation might actually be appropriate.

This initial broad-based strategy allows a series of future studies that might focus on particular groups of nutrients or eventually a selective series of active components. However, at this time it is not known whether a subset of components will be effective or whether a mixture of a broad range of nutrients will be required to maximize clinical effectiveness. To those who are concerned that it is not known which of the 36 nutrients is "the important one," we would say that the likelihood of finding a single effective ingredient is very small. Our future research will, in fact, be attempting to decrease the number of ingredients, in part to reduce the bulk of the supplement. For now, the complexity of the formulation should not detract from the treatment findings and, indeed, might be one of its strengths. Similarly, the doses of the individual ingredients of the nutritional supplement were quite high, again to maximize the chances of observing a clinical response, with the expectation that it may be possible in the future to lower the doses as a result of subsequent studies.

These data also have many strengths. First, the 11 cases in the completer analysis were unselected: they were the first 11 patients with bipolar disorder who were assessed systematically and followed for a minimum of 6 months. Also, in spite of receiving optimal psychiatric care, these were patients who were still symptomatic (or, in the case of patient 11, uncomfortable with the side effects of their medications). No problematic adverse effects were encountered from the nutrient supplement. Patients generally reported a subjective sense of improved well-being when taking the supplement, and several patients described this

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well-being as feeling more normal than what they had experienced with psychotropic medication.

Safety

Vitamin toxicity is a serious consideration when high doses of these substances are administered on a chronic basis. Patients with any known metabolic disorder (Wilson's disease, hemachromatosis, etc.) were excluded from this protocol. However, the assurance of safety of this supplement for any healthy patient is not something that can be precisely stated at this time. Prospective studies to establish an intake associated with toxicity of vitamins and minerals are not studies that have been, or even ethically can be, conducted. Data can be collected only from case studies of individuals who medicate themselves, or have ingested large quantities, and toxicity predicted to a very limited extent from animal studies. Additional problems in trying to set a level of intake arise from the knowledge that the bioavailability of some vitamins and most minerals depends on the rest of the foods in the diet, the presence of other dietary nutrients, the nutritional status of the individuals (absorption is significantly reduced when status is inadequate), and an individual's genetic makeup.

The levels of several ingredients might raise some questions regarding potential toxicity. Vitamin A is present in the supplement at a daily intake of 13,332 IU, or about 4 times the recommended daily intake, but chronic toxic reactions would not be expected at dosages less than 100,000 IU/day in adults with normal liver function.[37] Pregnant and lactating women are excluded from our protocols because of uncertainty about fetal exposure. Vitamin D in the supplement is present at a daily level of 1600 IU (40 μg) in the form of cholecalciferol, and in adults vitamin D toxicity usually does not occur unless intakes exceed 50,000 IU/day.[38] Vitamin B_{12} is provided in the supplement at 1000 μg/day, but there has been no reported toxicity associated with intakes of vitamin B_{12} at levels 1000 times the recommended daily intake of 6 μg/day; this is probably because the absorption decreases as body stores of vitamin B_{12} increase. Animal studies have demonstrated no adverse effects of vitamin B_{12}, even when administered by injection in very large doses.[39] Selenium in the supplement provides 400 μg/day in the form of a selenium amino acid chelate; studies have indicated that there are no clinical signs of selenosis at intakes of 853 μg/day.[40] Chromium is supplied in the supplement at 1000 μg/day. As there are no reported case studies available on toxicity, its ingestion even at high doses is generally not considered a risk.[41]

Overall, none of the ingredients of this supplement are present at levels that pose any apparent risk to healthy, nonpregnant adults. On the other hand, supplementation with dietary minerals and vitamins that significantly exceed the recommended daily intakes carries with it an unknown risk, and therefore the long-term safety of the nutritional supplement used in this study cannot be definitively proven. Patients undergoing clinical trials of this supplement should be monitored for adverse reactions and general health, just as they are when undergoing a trial of a new psychotropic medication.

Mechanisms of Action

An important question to address is *why* a broad-based nutrient supplement might improve mental health. There are at least 2 issues to consider:

1. Nutrient deficiencies influencing brain function. That there is a genetic predisposition to bipolar disorder is fairly well accepted.[42] The question is, what do those genes do? It is possible that bipolar disorder is an inborn error of metabolism, analogous to others such as phenylketonuria in which metabolic "errors" lead to altered brain function, but whose symptoms become clinically evident long after birth. If this is the case, the fact that a nutritional supplement may partially correct that metabolic error suggests that the predisposing genes are coding for proteins involved in metabolic pathways dependent on some of those nutrients. Many minerals (e.g., zinc) are important in dozens of biochemical pathways vital to brain function, so this observation provokes many questions about the specific mechanisms by which predisposing genes might affect mental health.
2. Nutrient deficiencies in the food supply. In view of the wide range of biological variability in humans, it is certainly feasible that different individuals have variable vulnerabilities to diverse nutritional deficiencies. An amount of dietary mineral intake that is sufficient for most of the population may be borderline-adequate, deficient, or even toxic for a minority.

Although the claim that the nutrient content of our food supply is decreasing is often made but not substantiated by health food publications, there is actually a small amount of valid scientific data supporting this contention. Mayer[43] compared the mineral content of 20 fruits and 20 vegetables from 1936 to the 1980s using a laborious methodology to ensure that comparable laboratory methods were employed. Mayer's results were sobering: over that 50-year period, there were statistically significant decreases of calcium, magnesium, copper, and sodium in vegetables and of magnesium, iron, copper, and potassium in fruits. Zinc was not studied. The magnitude of some changes was large: for instance, the copper level in vegetables in the 1980s was less than 20% of the 1936 levels. As Mayer pointed out, the changes should not be surprising, as agriculture relies on fertilizers containing only nitrogen, phosphorous, and potassium, and there is little effort to remineralize the soil over the decades.

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CONCLUSION

Regardless of the mechanisms involved, the findings reported here suggest that the amelioration of mood instability with broad spectrum nutritional interventions warrants further exploration.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), benztropine (Cogentin and others), bupropion (Wellbutrin and others), carbamazepine (Tegretol, Carbatrol), chlorpromazine (Thorazine and others), citalopram (Celexa), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clonidine (Catapres and others), clozapine (Clozaril and others), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), diazepam (Valium and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), fluvoxamine (Luvox), gabapentin (Neurontin), haloperidol (Haldol and others), lamotrigine (Lamictal), levothyroxine (Synthroid and others), lorazepam (Ativan and others), methylphenidate (Ritalin and others), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), pemoline (Cylert), propranolol (Inderal and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), trazodone (Desyrel and others), trifluoperazine (Stelazine and others), trimipramine (Surmontil), valproic acid (Depakene and others), venlafaxine (Effexor), zolpidem (Ambien).

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Appendix 1. Supplement Facts: E.M.Power+ (serving size = 8 capsules, taken 4 times per day for study protocol)[a]

Ingredient	Amount Per Serving	% Daily Value
Vitamin A (as retinyl palmitate)	3333 IU	67
Vitamin C (as ascorbic acid)	250 mg	417
Vitamin D (as cholecalciferol)	400 IU	100
Vitamin E (as *d*-alpha tocopheryl succinate)	100 IU	333
Vitamin B_1 (as thiamine mononitrate)	5 mg	333
Vitamin B_2 (as riboflavin)	5.5 mg	324
Vitamin B_3 (as niacinamide)	25 mg	125
Vitamin B_6 (as pyridoxine hydrochloride)	7 mg	350
Vitamin B_9 (as folic acid)	400 µg	100
Vitamin B_{12} (as cyanocobalamin)	250 µg	4167
Biotin	25 µg	8
Pantothenic acid (as *d*-calcium pantothenate)	6 mg	60
Calcium (as calcium complex,* calcium amino acid chelate)	550 mg	55
Iron (as iron amino chelate, iron complex*)	6 mg	33
Phosphorous (phosphorous complex)	350 mg	35
Iodine (from kelp)	75 µg	50
Magnesium (as magnesium amino acid chelate, magnesium complex)	250 mg	63
Zinc (as zinc amino acid chelate, zinc complex*)	20 mg	133
Selenium (as selenium amino acid chelate, selenium complex*)	100 µg	143
Copper (as copper amino acid chelate, copper complex*)	3 mg	150
Manganese (as manganese amino acid chelate, manganese complex)	4 mg	200
Chromium (as chromium amino acid chelate, chromium complex*)	250 µg	208
Molybdenum (as molybdenum amino acid chelate, molybdenum complex)	66 µg	88
Potassium (as potassium complex*)	100 mg	3
And a proprietary blend of the following**: *dl*-Phenylalanine, glutamine (as *l*-glutamine), citrus bioflavonoids (from peel), grape seed (*Vitis vinitera)*, choline (as choline bitartrate), inositol, *Ginkgo biloba* (from leaf), methionine (as *l*-methionine), germanium (as *Germanium sesquioxide)*, boron (as boron amino acid chelate), vanadium (as vanadium amino acid chelate, vanadium complex*), nickel (as nickel amino acid chelate, nickel complex*)		
Other ingredients: gelatin, magnesium stearate, microcrystalline cellulose, silicon dioxide		

[a]Manufactured for The Synergy Group of Canada, by Evince International, Farmington, Utah.
*Saccharide complex.
**Daily value not established.

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