Title: Multinutrients as Adjunctive Treatment for Bipolar Disorder: A randomized-controlled trial feasibility study

Key words: micronutrients, fish oil, bipolar disorder, randomized controlled trials, Adjuvant therapy, alternative medicine, nutrition, mental health

Lewis Mehl-Madrona, MD, PhD [a, b, c]
Email: lewis.mehlmadrona@maine.edu

Patrick McFarlane, LCSW, PMH-NP, FNP [c]
Email: Patrick2042np@gmail.com

Astha Kakkad MD, MSPH [b]
Email: akakkad@ northernlight.org

Samreen Fathima, BDS, MPH [b]
Email: sfathima@ northernlight.org

[a] Northern Light Acadia Psychiatry Residency, 268 Stillwater St., Bangor, Maine 04401, USA
[b] Clinical Research Center, Northern Light Eastern Maine Medical Center, 489 State St, Kelley 5, Bangor, ME, 04401, USA
[c] Coyote Institute, PO Box 39, Orono, ME 04473
*Corresponding author: PO BOX 39, Orono, ME 04473, USA
Tel: (+1) 808-772-1099; Fax: (+1) 207-406-5354.

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Abstract

Introduction: An open label trial showed reduction in symptoms from a comprehensive micronutrient supplement in combination with Fish Oil for adults diagnosed with bipolar disorder.

Methods: A double blinded, randomized, controlled feasibility trial explored the parameters necessary to mount a larger trial. We randomized in a 3:2 ratio to multinutrients or Placebo. We recruited patients diagnosed with bipolar disorder from a family medicine residency clinic. Diagnoses were confirmed via psychiatric interview. The primary outcome measure was change on a composite z-score of the clinical global impressions scale (CGI), the UKU Side Effects Scale, and medication doses.
Results: A total of 69 patients were randomized and data was analyzed for 49 patients. The mean difference of the composite z-score for the multinutrient group was 0.63 (SD; 0.25) and for the Placebo Group 0.47 (SD=0.22). Independent samples t-testing gave a t-score for that difference of 2.429 ($p = 0.019$; ES = 0.437; 95% CI = -0.556 to -0.053). Significantly more patients in the multinutrient group improved on the CGI ($p = 0.04$; OR = 4.0; 52% responders vs. 22% in the Placebo Group). All patients improved on the secondary measures with inter-group differences favoring the multinutrient group that did not reach statistical significance. The only adverse events occurring more among the multinutrient group were nausea and loose stools but these were not statistically significant between groups.
Conclusions: Multinutrients show promise for adjunctive treatment of bipolar disorder. We observed benefits for patients from closer surveillance, medication adjustment (mostly reduction), and increased human contact.

Introduction

There are compelling reasons to explore the role of nutrition in the treatment of psychiatric disorders. First, psychiatric disorders are prevalent and costly to families and society [1]. Second, two important studies have cast doubt on the efficacy of the long-term reliance on psychiatric medication [2, 3] for patients with psychotic disorders.

Bipolar disorder is a common neuropsychiatric illness with high rates of morbidity and mortality [4]. Despite available medications to treat bipolar disorder, recurrence rates are high [5]. Bipolar disorder is conventionally treated with typical or atypical antipsychotic medications, anti-epileptic medications, and/or lithium. The risks of atypical antipsychotic medications are well described and include the increased risk of acute kidney injury [6], cataracts [7], decreased cognitive function [8], increased risk for myocardial infarction and stroke [9], metabolic syndrome and type 2 diabetes mellitus [10], and dyslipidemia [11]. Anticonvulsant medications can cause encephalopathy and varying degrees of liver damage, even lethal [12]; hypothyroidism [13]; increased fracture risk [14]; mental sluggishness; falls; coordination problems; and aplastic anemia [15]. Lithium is associated with increased risk for acute and chronic kidney injury, hypothyroidism [13], and increased cancer risk [16, 17]. Lithium's classic "cognitive dulling" effect, with mild impairments in memory, information processing speed, and creativity, has also been empirically confirmed [18]. Relatedly, mortality rates are elevated among people with bipolar disorder compared to the general population. Men with the diagnosis of bipolar disorder live, on average 13.6 years less than the general population, and for women, 12.1 years less [19].

Firth et al. identified 33 metanalyses of placebo controlled RCTs, with primary analyses including outcome data from 10,951 individuals. The strongest evidence was found for polyunsaturated fatty acids (PUFAs) (particularly as eicosapentaenoic acid) as an adjunctive treatment for depression. Evidence suggested that PUFAs could also be beneficial for attention deficit/hyperactivity disorder, with no evidence for benefit in schizophrenia. Positive effects from RCTs of high dose methylfolate were found for major depressive disorder. Nacetylcysteine appeared to be a useful adjunctive treatment in mood disorders and schizophrenia. All nutrient supplements had good safety profiles, with no evidence of serious adverse effects or contraindications with psychiatric medications [20]. Blampied et al. reviewed double-blind, randomized controlled trials (DBRCTs) testing formulas including at least four vitamins and/or minerals used for the treatment of symptoms of anxiety, stress, or depression in adults not currently taking medication for psychiatric difficulties. The majority of the 23 trials reviewed were conducted on people without psychological difficulties, limiting the generalizability of the results in people with diagnosed mood and anxiety difficulties. Sixteen studies demonstrated positive effects for symptoms of anxiety, depression, or stress [21]. Later, Blampied et al. studied 150 adults with functionally impairing symptoms of anxiety/depression randomly assigning them to micronutrients or placebo for 10 weeks. Linear mixed-effects modelling showed significant improvements in both groups, with the micronutrient group improving significantly more quickly on both the Patient Health Questionnaire-9 (PHQ-9) ($t = -2.17$, $p = 0.03$) and the Generalized Anxiety Disorder Scale-7 (GAD-7) On the Clinical Global Impression-Improvement Scale (CGI-I), there were no group differences at end-point with 49 % of the micronutrient and 44 % of the placebo groups being identified as responders. Participants on micronutrients had significantly increased bowel motions compared with placebo. There were no serious adverse events [22]. Johnstone et al. conducted a meta-analysis focused on RCTs of multinutrients consisting of at least four vitamins and/or minerals as interventions for participants with psychiatric symptoms. They found 16 RCTs with 1719 participants in six psychiatric categories: depression, post-disaster stress, antisocial behavior, behavioral deficits in dementia, attention-deficit/hyperactivity disorder, and autism. Only the Attention-Deficit/Hyperactivity Disorder (ADHD) category was eligible for meta-analyses. In ADHD populations, statistically and clinically significant improvements were found in

global functioning, clinician ratings of global improvement, ADHD improvement, and clinician (but not observer) measures of ADHD inattentive symptoms. Narrative synthesis revealed a pattern of benefit for global measures of improvement in autism and in participants with behavioral deficits in dementia. Post-natural disaster anxiety and the number of violent incidents in prison populations also improved. Broad-spectrum formulas (vitamins + minerals) demonstrated more robust effects than formulas with fewer ingredients [23].

The adjunctive use of micronutrients benefited patients with depression [24]. One hundred years of scientific research has provided promising (though modest) results of using single nutrients to modulate mood swings and irritability [25]. In contrast, research since 2000 on formulas with more than 25 minerals and vitamins (referred to as broad-spectrum) have shown medium between-group effect sizes [26]. Over 20 RCTs have shown that adding micronutrients provides benefit by reducing the impact of stress; reducing anxiety and aggression; and improving mood, irritability, and inattentiveness [27]. One RCT showed that a 25-ingredient micronutrient formula plus some omega-3 fatty acids (EPA and DHA) was associated with a one-third reduction of aggressive offenses in young adult prisoners [28]. In another setting, micronutrients supplementation had a statistically significant impact on emotions of stress related to the 6.3 magnitude earthquake on February 22, 2011, in Christchurch, NZ [29]. These post-disaster results were replicated in a general population following a destructive flood in southern Alberta, Canada [30]. Almeida et al. conducted a randomized, controlled trial of adding B-vitamins to citalopram versus placebo [31]. No differences were found at 12 weeks but the odds ratio of remaining in remission at 52 weeks was 2.49, favoring the B-vitamin group over the placebo group, showing that the effects of multi-nutrients might be longer-term than the usual expectations for medications.

An RCT with a broad-spectrum formula in adults with ADHD [32] showed greater reductions in symptoms from those taking placebo, with medium-to-large between-group effect sizes. In a subgroup that entered the trial with moderate to severe depression, twice as many people went into remission in the micronutrient group compared to the placebo group. Importantly, the benefits of micronutrients continued through the 1-year follow-up [33]. Rucklidge et al. conducted a blinded, randomized controlled trial of medication-free children with ADHD (7–12 years) assigned to either multi-nutrients or placebo for 10 weeks [34]. Intent-to-treat analyses showed significant between-group differences favoring micronutrient treatment on the Clinical Global Impression (ES = 0.46), with 47% of those on micronutrients identified as 'much' to 'very much' improved versus 28% on placebo. According to clinicians, 32% of those on micronutrients versus 9% of those on placebo showed a clinically meaningful improvement on inattention, but no group differences on hyperactive-impulsive symptoms (OR = 1.0; 95% CI: 0.4–2.5). Based on clinician, parent, and teacher report, those on micronutrients showed greater improvements in emotional regulation, aggression and general functioning compared to placebo (ES ranged 0.35–0.66).

In an open-label trial that compared 19 patients who were willing to take micronutrients over 24 months to a convenience sample from the same practice, Mehl-Madrona et al [35] found reduced doses of medication and reduced number of side effects with equivalent symptom relief among patients diagnosed with psychotic disorders compared to similar patients who were not supplemented. We used EMPowerplus™ (EMP), a broad-spectrum micronutrient formula. The safety and tolerability of EMP has been assessed by Simpson et al., 2011. All clients were evaluated with the Positive and Negative Symptom Scale and the Clinical Global Impression scale at study baseline and after 3, 6, 9, 12, 15, 18, and 24 months. Psychosis was confirmed with clinical interview using DSM IV-TR criteria. All participants had normal physical examinations and laboratory studies. Outcomes were similar for both groups until 15 months, though the micronutrient group used significantly less antipsychotic medication throughout that time ($p < 0.001$). At 15 months, the micronutrients + medication group began to exhibit fewer symptoms than the medication-only group, a difference that increased at 24 months. We concluded that

improved nutrition using micronutrients among people with psychotic disorders allowed them to achieve similar effectiveness at lower doses of medication and fewer side effects than those who didn't receive supplements.

There are roughly 90 years of scientific literature demonstrating the relevance of dietary nutrients for mental health, forming the rationale for including the use of micronutrients. Some of the earliest research studies on nutrients relevant to mental illness observed irritability and mood problems in people known to be deficient in the B vitamins [36], as well as reporting positive improvements in mental illness when treated with such nutrients as manganese [37, 38] and nicotinic acid [39], regardless of whether or not they were deficient in said nutrients. Although interest in such studies has declined since the introduction of psychiatric medications in the 1950s, recent work on folic acid (vitamin B9) suggests that low levels may be associated with depressive symptomatology and poor response to antidepressant medication [40, 41]. Further discussion follows in our background and significance section at the end of this proposal.

We wondered if adjunctive micronutrient treatment would permit lower doses of conventional medications to be effective for bipolar disorder with fewer side effects. Many of the side effects of conventional medication are dose-related, so dose reductions can benefit patients in lowering risk for morbidity and mortality. Micronutrients are relatively safe compared to conventional medications and could make a significant difference in the quality of life of patients with bipolar disorder.

Methods.

Trial Design, Participants, and Setting: This was a double-blind, randomized controlled trial that intended to assign 120 stable adult outpatients (age >= 18) with bipolar disorder, type 1 or 2 (DSM-5 criteria) to supplementation with a 36-ingredient vitamin/mineral formula and an omega-3 fatty acid supplement (N=72) or to matched double placebo (N=48) in a 3:2 ratio for a study duration of one year. This ratio was chosen to improve recruitment, expose fewer participants to placebo, and obtain essentially the same power as a 1:1 ratio. The population was largely federally funded through Medicare or Medicaid, was white with 1 Native American (reflective of the population of Maine, was rural, and was predominantly female (65%). All participants received care at the Northern Light Family Medicine Residency Clinic in Bangor, Maine. Participants were excluded if they were medically or psychiatrically unstable (until stabilized), had mineral-related illnesses, had hypervitaminosis, had chronic kidney disease of stage II or higher, were unable to communicate in English or French, or were pregnant. The only exclusions occurred for pregnancy (n=2)

Blinding and Randomization. One research coordinator who did not have contact with participants was unblinded so she could dispense appropriately for each participant. All research and clinical staff and all patients were blinded to the study drug. Placebo drug appeared identical to the active micronutrients. The placebos were manufactured by True Hope for the multi-nutrient and Wiley's Finest Fish Oil for the fish oil. Olive oil was used for the fish oil placebo. Low dose riboflavin was added to the multi-nutrient placebo to change urine color to mimic that obtained from active multi-nutrient dosing. No adverse events led to the Data Safety Monitor breaking the blind. Randomization was accomplished using a random number generator for which the integers 1,2, and 3 assigned participants to the active group and 4 and 5 to the placebo group. Assignment envelopes were prepared before enrollment commenced.

Sample Size

We used the G*3 Power software from the University of Dusseldorf to calculate sample size for repeated measures analysis of variance and determined that we needed 97 patients for a conservative effect size estimate of 0.4 to obtain 80% power to detect an effect.

Primary Intervention

We assessed participants monthly and provided them with EMPowerplus™ and Wylie's Finest Alaskan Fish Oil or placebos. We started with 2 capsules twice daily with meals and increased monthly by 2 capsules twice daily to achieve a maximum dose of 8 capsules twice daily at month 4 as this was the dose that we used in previous studies (Mehl-Madrona, et al., 2010; Mehl-Madrona & Mainguy, 2017, 2018). We chose the 2100 mg dose of EPA in the fish oil (three capsules), since 2000 mg was the threshold dose for improving symptoms among people diagnosed with schizophrenia (Peet, et al., 2002). Nagakura, et al. (2000) used 28.6 mg/kg EPA among children with asthma, which corresponds to 1876 mg for a 70 kg adult. The American Heart Association recommends EPA as preventative (Siskovich, et al., 2018) and reviews studies that use as high as 8 gm/day without adverse events.

Measures

The primary outcome variable was a composite z-score calculated from three separate z-scores for medication dosage (measured in haloperidol equivalents, valproic acid equivalents, lithium dose, sertraline equivalents, or lorazepam equivalents), the CGI score, and the UKU total side effect score [42]. We converted doses of antipsychotic medication to haloperidol equivalents using standardized conversion formulas that we [35] used in previous research [43]. We found the maximum recommended dose for each anticonvulsant from the manufacturers' web sites and converted patients' doses to a proportion of the maximal dose, combining portions when patients took more than one anticonvulsant and then converted proportions back to valproic acid dosages. We used the same approach for antidepressants and benzodiazepines. The other medications required were sufficiently infrequent as to not requite conversion to another medication. Z-scores were calculated for each class of medication and then combined to obtain a z-score for all medication changes. Changes in the UKU Side Effects Profile were also converted into z-scores. The composite z-score was obtained by adding the three component z-scores and dividing by 3. We used an intent-to-treat approach for any patient who had available data after the month 1 time point. Differences in change in composite z-scores were assessed using an independent t-test.

Composite z-scores are often used when an outcome is multifactorial with measures of each factor being on different scales – in this case, outcome ratings from 1 to 7, changes in medication dosage, and side effects. For example, Giamarellos-Bourboulis et al. used a composite z-score in a study of community-acquired pneumonia in which the outcome measure combined a respiratory severity scale and the score on the Sequential Organ Failure Assessment [44]. Gewandter et al. discuss the use of composite z-scores in pain trials where pain level, medication levels, and psychological outcome measures are combined [45]. Song et al. discuss the advantages and mathematical properties of composite z-scores [46].

The secondary endpoints were (1) Number of ED visits for psychiatric reasons and all reasons (2) Number of hospitalizations for psychiatric reasons and all reasons, (3) Scores on the Positive and Negative Symptom Scale, (4) Scores on the Young Mania Scale, (5) Scores on the My Medical Outcomes Profile version 2 (MYMOP-2), (5) Scores on the Hamilton Anxiety Scale, (6) Scores on the Montgomery-Asburg Depression Rating Scale (MADRS), (7) changes in vital signs, including BMI and waist circumference, and (8) Scores on the Mini-Nutritional Assessment Scale.

CGI-BP. The CGI is one of the most widely used brief assessment tools in psychiatry and is a 3-item observer-rated scale that measures illness severity (CGIS), global improvement or change (CGIC) and therapeutic response [47]. The illness severity and improvement sections of the instrument are used more frequently than the therapeutic response section in both clinical and research settings. The CGI has proved to be a robust measure of efficacy in many clinical drug trials, and is easy and quick to administer,

provided that the clinician knows the patient well. We used the bipolar version and assessed change from the worst phase of the illness and from the level of severity at enrolment in the study for depression, mania, and total severity of illness. The CGI is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill patients). CGI scores range from 1 (very much improved) through to 7 (very much worse).

UKU Side Effects Scale. The UKU (Udvalg for Kliniske Undersogelser, Scandinavian Society for Psychopharmacology) Side Effect Rating Scale is an often used comprehensive tool which has been extensively validated [48]. Assessment of severity scores of individual symptoms is accomplished with a structured interview during which the scale is completed item by item. The UKU Side Effect Rating Scale has both a patients' self-assessment scale (UKU-SERS-Pat) for side effects and a clinicians' ratings scale (UKU-SERS-Clin). It provides a total score and sub-scores of Psychic, Neurological, Autonomic and Other side effects. It comprises ratings (0 to 3) of 48 single items, a global assessment of the influence of the reported side effects on daily performance, and a statement of the effects of the adverse events on continuation of the medication. Patients report side effects more frequently and rated symptoms more severe than clinicians [49].

Positive and Negative Symptom Scale (PANSS). This is a 30-item, 7-point rating scale that adapted 18 items from the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) and 12 items from the Psychopathology Rating Schedule (PRS) of Singh and Kay (1975a). Each item on the PANSS is accompanied by a complete definition as well as detailed anchoring criteria for all seven rating points, which represent increasing levels of psychopathology: 1 = absent, 2 = minimal, 3 = mild, 4 = moderate, 5 = moderate-severe, 6 = severe, and 7 = extreme. Seven parameters form a Positive Scale, seven a Negative Cale, and 16 a General Psychopathology Scale. The scale has been widely determined to be reliable and valid and compared to other similar scales [50-53].

Young Mania Rating Scale. This 11-item observer-rated instrument is scored based on a brief interview. Higher scores on items and total scores reflect greater abnormality and severity of signs and symptoms. All items have five anchor points; in seven items these are scored 0–4 and in four they are scored 0–8. The range of total scores is 0–60. When several keys are given for a particular grade of severity, the presence of only one is required to qualify for that rating. The keys provided are guides; One can ignore the keys if that is necessary to indicate severity in exceptional cases. Reliability and validity have been well-established [54] and it is widely used in studies of mood disorders and bipolar disorder [55]. Rabinowitz et al. have confirmed the validity and reliability of the YMRS as recently as 2024 and have identified ways to further improve these parameters [55]

My Medical Outcomes Profile Version 2. The Measure Yourself Medical Outcome Profile is designed to prioritize and measure changes important to a person/patient. The MYMOP instructs patients to "Choose 1 or 2 symptoms that bother you the most." Patients then consider these symptoms individually, ranking the severity of symptoms over the past week with a zero indicating "as good as it could be" and a 6 indicating "as bad as it could be." Using the same scale, the person is directed to "Choose 1 activity (physical, social, or mental) that is important to you, and that your problem makes difficult or prevents you from doing. Score how bad it has been in the last week." These questions are repeated later, supplying the patient with the symptoms and activity chosen at the first time point. MYMOP® was validated against the Short Form Health Survey (SF-36) in 1996 [56]. The MYMOP® is scored by comparing change in mean score for each question. The MYMOP® profile score is calculated by comparing the average of the changes in individual component mean scores [57].

Hamilton Anxiety Scale. The HAM-A has undergone numerous revisions that have resulted in at least three different versions of the scale [58] and three structured interview guides [59]. In its original form,

the HAM-A was posited to yield a general unipolar anxiety dimension as well as two correlated "psychic" and "somatic" anxiety factors [60]. Research examining the Hamilton scale has generally replicated the original's two-factor structure [61]. Others have replicated this solution with minor inconsistencies (e.g., a single indicator cross-loading on each of the factors; [62]). Two studies with different patient populations that reported using the original Hamilton scale observed three-factor solutions reflecting anxiety, depression, and somatic factors among an outpatient clinical sample which are reliable and valid [63].

Montgomery-Asburg Depression Scale. Depressive symptoms were measured using the semi-structured interview of the Montgomery–Asberg Depression Rating Scale (MADRS; [64]. The MADRS is a 10-item interviewer-rated questionnaire, comprising a 7-point Likert scale, with specific anchors for each item. For example, item 1, "apparent sadness", is defined as "representing despondency, gloom, and despair, more than just ordinary transient low spirits reflected in speech, facial expression, and posture". Instructions ask the interviewer to "rate by depth and inability to brighten up". Items are rated on the following scale, with intermediate scores permitted: 0=no sadness; 2=looks dispirited, but does brighten without difficulty; 4=appears sad and unhappy most of the time; and 6=looks miserable all the time; extremely despondent. The MADRS total score ranges between 0 and 60, with higher scores indicating more severe symptoms. Hernimann et al. have further confirmed the reliability and validity of the MADRS [65].

Mini-Nutritional Assessment Scale. Mini Nutritional Assessment Test recommended by "European Society of Parenteral and Enteral Nutrition" (ESPEN) is a rapid method taking approximately 10-15 minutes. Developed by Vellas et al. [66], this method is widely used throughout the world. Mini Nutritional Assessment Test has 2 sub-dimensions as scanning and assessment and consists of 18 items in total. Cronbach's α coefficient has been found to be 0.842 [67].

BASIS-24. The BASIS-32 was developed in 1984 to meet the need for a brief, but comprehensive mental health status measure that would be useful in assessing outcome of mental health treatment from the consumer's point of view. It is a measure of self-reported difficulty in 5 major symptom and functioning domains: daily living/role functioning skills, relation to self/others, depression/anxiety, impulsive/addictive behavior, and psychotic symptoms [68]. It was reduced to 24 questions in 2004 by Eisen et al. who found good reliability and validity [69].

Statistical Methods

We used the Statistical Package for the Social Sciences (SPSS) for descriptive statistics, repeated measures analysis of variance, linear mixed modeling, independent t-test, Wilcoxin signed rank test, and chi-square analyses. The baseline composite z-score was subtracted from the ending composite z-score and those differences were compared using independent samples t-testing. We also compared changes in the scores of all outcome measures between the two treatment groups using linear mixed modeling, repeated measures analysis of variance, the chi-square test, and the Wilcoxin signed rank test.

Results.

Study Population Characteristics

Figure 1 presents the CONSORT flow diagram for the study including numbers in each category. Table 1 presents the reasons why people who were randomized withdrew from the study before the one month first data collection time. More people left the active intervention than the placebo, but none because of adverse effects of the nutrients. Table 2 provides the baseline demographic data for our participants. There were no significant differences between the groups for baseline demographics. There were no statistically significant differences in any of our outcome measures between members of the two groups at baseline.

Outcome Measures

The mean difference of the composite z-score for the multi-nutrient group was 0.63 (SD; 0.25) and for the Placebo Group 0.47(SD=0.22). Independent samples t-testing gave a t-score for that difference of 2.429 (p = 0.019; Effect Size = 0.437; 95% CI = -0.556 to -0.053). Significantly more patients in the multi-nutrient group improved on the CGI over the course of their participation in the study (p = 0.04; OR = 4.0; 52% responders vs. 22% in the Placebo Group). All patients improved on the secondary measures with inter-group differences favoring the multi-nutrient group that did not reach statistical significance. Linear mixed modeling procedures did not improve on these results. The only adverse events occurring more frequently among the multi-nutrient group were nausea and loose stools, but these were not statistically significant between groups.

Table 3 shows the results of non-parametric analysis. For the individual components of the primary outcome measure, the Multi-Nutrient Group showed statistically significantly more instances of improvement than the Placebo Group (p = 0.042; OR = 4) on the CGI, but not on side effects or changes in medications. Repeated measures analysis of variance showed similar results. The blinded research team were unable to accurately guess group assignment (51% wrong).

Table 4 shows the changes in time in the CGI-BP rating of severity of illness assessed at the 3-month period from baseline to 12 months assessed. Average improvement from baseline to six months (time 3) was statistically significant for all participants (time 3). Improvement leveled at six months and remained statistically significantly better than baseline throughout. Substantial improvement occurred in all measures over time with most of the improvement completed by six months (hence, the lack of significance of the “change in the last month” on the CGI. Table 6 shows changes in medication use over time. The reduction in medications for all participants was statistically significant over time for antipsychotics, anticonvulsants, and antidepressants.

Interactions. There was a statistically significant interaction of the MYMOP Wellbeing Scale with education (F = 5.368; p = 0.003) with higher education being associated with greater wellbeing. There was no interaction with other demographic variables.

Cost. The cost per completed subjects averaged $7102.00. Thirty-seven percent of those costs were spent on direct research and 63% spent on regulatory matters related to the FDA and to our IRB.

The only hospitalization occurred in a participant who discovered her husband having sex with another woman and went to the Emergency Department to request an overnight observation admission as a preventive measure. She stayed for one night and was in the placebo group. No emergency department visits were related to multi-nutrient use and no significant differences were noted in number of E.D. visits between groups.

Discussion.

We found statistically significant improvements in the primary outcome variable in favor of multi-nutrients. The patients in this setting were symptomatic at a level below needing hospitalization, but still distressed. Significantly more patients in the multi-nutrient group improved on the CGI over the course

of their participation in the study (p = 0.04; OR = 4.0; 52% responders vs. 22% in the Placebo Group). Receiving Multi-Nutrients was associated with consistent trends in favor of Multi-Nutrients that did not reach statistical significant on the secondary outcome measures.

Simply being in the study was associated with statistically significantly improvement in all measures. This suggests that patients with bipolar disorder in primary care settings are not seen sufficiently often and that increased frequency of visits could improve their symptoms. Family physicians sometimes forget the value of their person in the clinical encounter and regardless of whether medications were adjusted, the presence of the physician has value. The statistically significant improvement in all outcome measures for all patients combined was associated with significant reductions in medications and side effects. More frequent visits with lower doses of medications may be useful.

It was more difficult than we anticipated to retain subjects, presumably related to the number of pills that people needed to take. The cost per subject was also greater than we anticipated, primarily related to the increased regulatory requirements imposed by our Institutional Review Board (IRB). Since we conducted this study in a Primary Care setting, every Primary Care visit was seen as an Adverse Event, including falls on ice, insect bites, and strains and sprains. This produced many Adverse Events to report to the IRB.

Our primary care patients led complicated lives. They struggled with the social determinants of health, including lack of income, lack of employment, and lack of transportation. Another strategy would be to recruit only stable patients who do not struggle with these issues and then determine if their medication doses could be reduced when micronutrients are added. That might require multiple recruitment centers.

Clinical Significance. A comprehensive multi-nutrient formula alongside fish oil produced greater improvement in symptoms among people diagnosed with bipolar disorder than placebo, while at the same time allowing decreases in medication doses with reduced side effects. More frequent visits were associated with improvement for all participants.

Strengths and Limitations.

One strength of our study is its occurrence in a real-world primary care residency clinic with typical primary care patients encountered in such facilities. We were able to show that a randomized, clinical trial can be done in a residency clinic and to explore some parameters to make future studies more likely to be successful. Our study was limited by our under-estimation of the regulatory costs associated with each participant thereby limiting our total sample size and reducing power below what was desired. We also did not anticipate the Covid-19 pandemic which brought the study to a halt. We did not have a way to verify that participants were taking supplements in the dose prescribed. We also underestimated the degree of improvement that would come from participants having more regular visits (monthly) and greater attention to medication adjustments (primarily reductions).

Implications for Future Research

Further research is indicated. Future studies should anticipate enrolling a larger number of patients and following them for at least one year. Quantifying participant intake of multi-nutrients through an assay of at least one component would improve validity. A lead-in period of 4 months before randomization to determine if participants are willing to take the micronutrients over an extended period and to adjust and stabilize participants' medication regimens and doses could improve the ability to detect differences between multi-nutrients and placebo.

Conclusions.

Multi-nutrients appear useful for patients with bipolar disorder. Monthly visits to the family medicine clinic appear to be more helpful than the irregular, periodic check-ins that were occurring prior to participants'' enrolment in the study. Closer follow-up can benefit all patients diagnosed with bipolar disorder. A strategy of medication reduction when accepted by the patient was also successful, suggesting that sometimes higher doses of medication are less helpful than lower doses. Patients and doctors worked together to optimize doses, efficacy, and side effects, reflected in the statistical significance of the composite z-scores when the differences in the individual components did not meet the $p = 0.05$ level.

Figure 1. CONSORT Flow Diagram Micronutrients

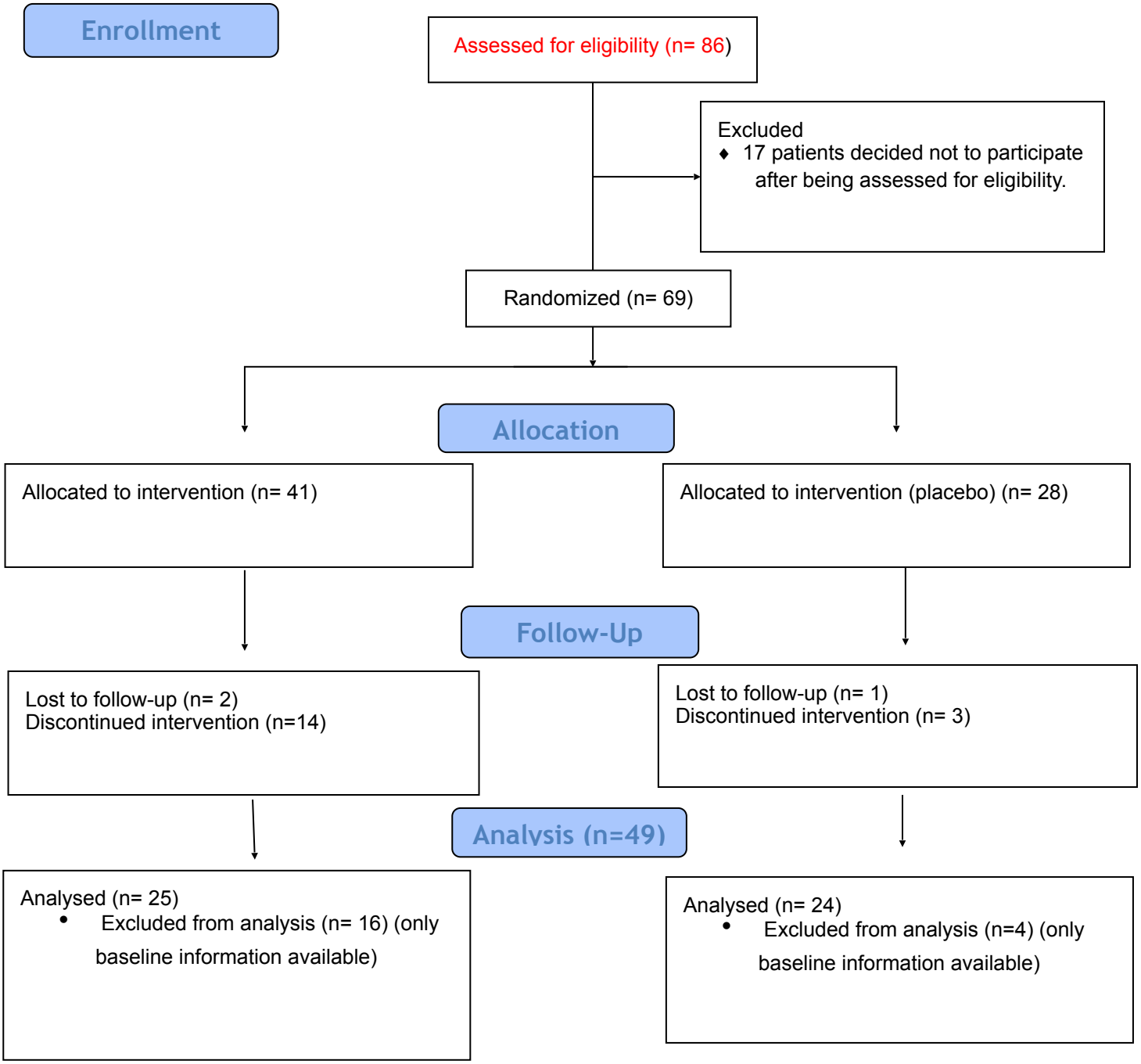

Table 1. Reasons for Discontinuation before the first follow-up appointment.

Intervention Group Reason	Number reporting Intervention Group	Placebo Group Number reporting
Moved/left practice/no answer to phone calls	8	1
Rejected possibility of taking placebo	2	0
Covid-19	1	0
Hives around neck	1	0
Ordered actual vitamins	2	0
Family problems/ too stressed	1	1
Too many pills	2	1

Table 2.	**Demographic Characteristics of the Participants**			
Measure	**Placebo (N= 24)**	**Intervention (N= 25)**	**Total (N= 49)**	***P* Value**
Age (mean ± SD)	40.61 ± 12.1	42.08 ± 13.6	41.39 ± 12.853	0.694[c]
Gender, No. (%)				
Male	10 (43.5)	8 (30.8)	18 (36.7)	0.390[d]
Female	13 (56.5)	18 (69.2)	31 (63.3)	
White race	23 (100)	25 (96.2%)	49 (100%)	1.000[d]
Education[e] No. (%)				
High school or less	8 (36.4)	13 (50.0)	21 (43.8)	0.393 [d]
College or graduate	14 (63.6)	13 (50.0)	27 (56.3)	
Marital Status No. (%)				
Married	5 (20.8)	8 (30.8)	13 (26.0)	0.360 [d]
Divorced	10 (41.7)	6 (23.1)	16 (32.0)	
Never married	9 (37.5)	12 (46.2)	21 (42.0)	
Social Support No. (%)				NS
Single	20 (83.3)	18 (69.2)	38 (76.0)	
Multiple	4 (16.6)	8 (30.8)	12 (24.0)	
Employed or Volunteer in past 30 days No. (%)				

Yes	13 (54.1)	14 (53.8)	27 (54.0)	NS
No	11 (45.8)	12 (46.2)	23 (46.0)	NS
Waist Circ[a](mean ± SD)	112.1 ± 45.8	103.42 ± 18.9	107.987 ± 35.492	0.459[c]
BMI[b](mean ± SD)	33.07 ± 10.8	33.51 ± 8.8	33.294 ± 9.713	0.879[c]
BP-Systolic (mean ± SD)	124.74 ± 18.6	121.04 ± 13.3	122.78 ± 15.927	0.423[c]
BP-Diastolic (mean ± SD)	76.61 ± 9.4	74.04 ± 10.1	75.24 ± 9.803	0.365[c]
Heart Rate (mean ± SD)	80.09 ± 12.9		78.73 ± 11.028	0.425[c]
Respiratory Rate (mean ± SD)	16.87 ± 1.6		16.37 ± 1.334	0.012[c]
Study Visits attended				
Less than or equal to 6	15 (66%)			NS
>6	10 (40%)			NS

[c] Independent samples *t*-test
[d] Fisher's Exact Test

Table 3. Results of Chi-Square Analysis			
Observation	**Placebo**	**Intervention**	**P Values**
	N= 24	N=25	
Study Visits attended			
• Less than or equal to 6	13 (59.2%)	15 (66%)	Chi-square = 0.298 p = 0.585
• >6	11 (40.8%)	10 (40%)	
Antipsychotic Med Usage			
• Decreased	7 (29.1%)	3 (12%)	Chi-square = 2.743
• Increased	0	3 (12%)	p = 0.098
• No Change	5 (22%)	9 (36%)	
• Not on Antipsychotics	12(48%)	10 (40%)	
CGI Scores (LOCF) (given monthly; change from baseline to end of study)			
• Responders	5 (22%)	13 (52%)	Chi square = 5.118
• Non-Responders	19 (35%)	12 (24%)	p = 0.023
• Worsened over the course of the study (included in non-responders)	10 (44%)	6 (24%)	
UKU Side Effects Total Scores			
• Improved	18 (78%)	22 (88%)	Chi-square = 1.187
• Worsened	4 (17.4%)	3 (12%)	p = 0.276
• No Change	1 (4%)	0	

Table 4. Differences in outcome measures over time for the entire group.

	Baseline Value	Difference Time 1 to 5	Standard Error	Significance	95% Confidence interval
CGI: Severity of Illness	3.82 + 0.92	1.131	0.147	< 0.001	0.836 to 1.427

CGI: Interval Change during the past month	3.62 + 1.16	0.417	0.220	0.064	-0.025 to 0.859
CGI: Change from Worst Phase of Illness	2.80 + 1.03	0.720	0.178	<0.001	0.361 to 1.078
MYMOP Symptom 1	4.48 + 1.25	3.921	0.182	<0.001	3.555 to 4.288
Basis-24 Score	61.12 + 9.09	4.620	1.249	<0.001	2.100 to 7.140
MADRS	18.3 + 8.61	6.886	1.344	<0.001	4.1555 to 9.576
Hamilton Anxiety	16.38 + 11.84	6.131	1.274	<0.001	3.562 to 8.700
Young Mania	19.45 + 4.6	2.835	0.850	0.002	1.126 to 4.544
Total UKU Side Effects	19.4 + 6.18	2.616	0.713	<0.001	1.180 to 4.052
UKU Neurological Side Effects	10.19 + 2.10	1.833	0.650	0.007	0.524 to 3.141
UKU Psychological Side Effects	13.14 + 6.66	4.936	0.907	<0.001	-6.759 to -3.113
UKU Autonomic Side Effects	5.18 + 4.35	-2.715	0.685	<0.001	1.337 to 4.093
UKU Side Effects – Other Symptoms	5.01 + 2.10	-1.810	0.240	0.008	0.477 to 3.112

Table 5. Comparisons between Groups (a minus sign favors the Multi-nutrient group) for the difference measured from the last data point collected to baseline.

Variable	Difference between groups	Standard Error	Significance	95% Confidence Interval
CGI: Severity of Illness	-0.413	0.235	0.085	-0.886 to 0.059
CGI: Change in the last month	-0.301	0.240	0.215	-0.784 to 0.181
CGI: Change from the Worst Phase of Illness	-0.093	0.145	0.525	-0.199 to 0.365
MYMOP Symptom 1	-0.115	0.142	0.422	-0.402 to 0.171
Basis-24 Score	-2.090	2.757	0.424	-7.501 to 3.214
MADRS	-2.143	2.663	0.425	-3.691 to 3.171
Hamilton Anxiety	-1.274	2.754	0.646	-4.264 to 6.812
Young Mania	-1.135	1.891	0.551	-4.93**6 to 2.667**
Total UKU Side Effects				

UKU Neurological Side Effects	-1.739	0.892	0.058	-0.059 to 3.536
UKU Psychological Side Effects	-0.593	1.926	0.759	-4.465 to 3.279
UKU Autonomic Side Effects	-1.157	1.231	0.352	-3.632 to 1.318
UKU Side Effects – Other Symptoms	-1.021	1.282	0.201	-2.117 to 2.390

Table 6. Changes in medication use over time.

Drug	Multinutrient Group, Beginning Dose	, Ending Dose	Placebo Group, Beginning Dose	, Ending Dose	Significance
Antipsychotics (chlorpromazine equivalents)	13 people, 334.8 mg	13 people, 151.0 mg	15 people, 307.6 mg	15 people, 196.0 mg	p = 0.17
Anticonvulsants (Valproate mg equivalents)	17 people, 786.7 mg	17 people, 631.2 mg	20 people, 525.7 mg	20 people, 497.9 mg	p = 0.073
Antidepressants (Sertraline mg equivalents)	14 people, 160.8 mg	14 people, 154.3 mg	20 people, 207.9 mg	20 people, 150.3 mg	p = 0.254
Lithium	4 people, 720 mg	4 people, 720 mg	3 people, 750 mg	3 people, 750 mg	NS
Hydroxyzine	5 people, 79 mg	5 people, 59 mg	5 people, 115 mg	5 people, 73 mg	NS
Opiates in morphine equivalents	5 people, 63 mg	5 people, 68 mg	8 people, 70 mg	8 people, 72 mg	NS
Psychostimulants in methylphenidate equivalents	4 people, 61.9 mg	4 people, 69.4 mg	6 people, 50.3 mg	6 people, 38.8 mg	NS
Requip	1 person, 1 mg	1 person, 0 mg	1 person, 3 mg	1 person, 3 mg	NS
Baclofen	5 people, 51 mg	5 people, 25 mg	2 people, 25 mg	2 people, 10 mg	NS
Buspirone	2 people, 37 mg	2 people, 10 mg	2 people, 15 mg	2 people, 15 mg	NS
Benzodiazepines in clonazepam equivalents	3 people, 8.6 mg	3 people, 8.6 mg	2 people, 3 mg	2 people, 0.75 mg	NS

Clonidine	4 people, 0.14 mg	4 people, 0.11 people	4 people 0.23 mg	4 people, 0.23 mg	NS

Discussion.

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