Successful Treatment of Bipolar Disorder II and ADHD with a Micronutrient Formula: *A Case Study*

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ABSTRACT

Bipolar disorder with co-occurring attention-deficit/hyperactivity disorder (ADHD) is a challenge to treat. Ten previous reports have shown potential benefit of a micronutrient treatment (consisting mainly of vitamins and minerals) for various psychiatric symptoms, including mood and ADHD. This case study aimed to investigate the longer term impact of the micronutrients on both psychiatric and neurocognitive functioning in an off-on-off-on (ABAB) design with 1 year follow-up. A 21-year-old female with bipolar II disorder, ADHD, social anxiety, and panic disorder entered an open-label trial using a nutritional treatment following a documented 8 year history of ongoing psychiatric symptoms not well managed by medications. After 8 weeks on the formula she showed significant improvements in mood, anxiety, and hyperactivity/impulsivity. Blood test results remained normal after 8 weeks on the formula. She did not report any adverse side effects associated with the treatment. She then chose to come off the formula; after 8 weeks her depression scores returned to baseline, and anxiety and ADHD symptoms worsened. The formula was reintroduced, showing gradual improvement in all psychiatric symptoms. This case represents a naturalistic ABAB design showing on-off control of symptoms. After 1 year, the patient is now in remission from all mental illness. Neurocognitive changes mirrored behavioral changes, showing improved processing speed, consistency in response speed, and verbal memory. A placebo response and expectancy effects cannot be ruled out although previous poor response to treatment and the duration of the current positive response decrease the likelihood that other factors better explain change. These consistently positive outcomes alongside an absence of side effects indicate that further research, particularly larger and more controlled trials, is warranted using this multinutrient approach.

INTRODUCTION

Estimates of the overlap between bipolar disorder and attention-deficit/hyperactivity disorder (ADHD) range from 57% to 93% in children[1,2] and while it is estimated that 10% to 20% of bipolar disorder adults also have ADHD,[3,4] the overlap in adults has not been adequately studied.[5] Co-occurring bipolar disorder and ADHD is associated with greater affect dysregulation, more depressive and mixed episodes, shorter euthymic periods between episodes,[4] and earlier onset of the first manic episode.[6] The two in combination are also associated with significantly greater neurocognitive impairments than either condition on its own.[7,8] It has also been well established that bipolar disorder in

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combination with ADHD can significantly impact response to treatments[9,10] with studies in pediatric populations showing modest responses to front-line treatments, with response estimate ranging from 20% to 29%.[11,12] There is no empirical data in the adult literature to assess how much ADHD impacts on the treatment of bipolar disorder; however, it is well established that co-occurring disorders significantly reduce treatment response in bipolar disorder.[13] Overall, empirical data supporting the use of specific medications for individuals with both bipolar disorder and ADHD are lacking in both the child[14,15] and adult literature.[4]

Even for those who do respond to medications, the side effects can often reduce their acceptability. Side effects of mood stabilizers include adiposity, cardiac changes, neuromuscular effects, hypokinesias, and hyperandrogenism.[16,17] Adverse effects of stimulants can include nausea, cardiovascular side effects, insomnia, and weight loss.[18] These side effects, in combination with the overall difficulty in treating both conditions, indicate the need to investigate other treatment options, particularly for those with complex psychiatric presentations.

It has long been known that behavioral/psychiatric symptoms can be a manifestation of nutrient deficiencies and there is a growing literature showing that a broad-based micronutrient intervention (such as combinations of minerals, vitamins, and amino acids) can be a successful alternative for the treatment of unstable mood, in both children and adults.[19] This approach is based on the logic that nutrients work together in the brain and humans require multiple nutrients in combination for optimal functioning. A growing number of case studies, open-label trials, and database analyses have been published showing clinically significant improvements in depression, mania, and general psychiatric status when using a micronutrient formula distributed under the name of Empowerplus (EMP+).[20-27] These positive studies provided the impetus to study the impact nutrients may have on individuals with both ADHD and mood instability. The case study reported here is of a 21-year-old female, KT (not her real initials), with both bipolar disorder and ADHD who was treated with EMP+ in an off-on-off-on (ABAB) natural design with a 1 year follow-up. Neurocognitive assessments at baseline and 1 year later were also included.

METHOD AND RESULTS

KT was first referred to a pediatric mental health service in 2000, at 12 years of age. She was involved with a number of psychiatric services for 5 years, with a variety of presenting concerns including ADHD, hypomania, depression, oppositional defiant disorder, and specific learning disabilities (math and spelling). During this time, she was mainly treated with methylphenidate and fluoxetine, neither of which she found beneficial for extended periods of time. In 2008, KT was recruited for an 8 week open-label trial of EMP+ for adults with ADHD and mood instability.[28] At the time she was contacted about the trial, she was not taking any medications for her psychiatric illnesses. The trial then extended into a natural ABAB design. The procedures were approved by the university and health and disability ethics committees. Written consent was obtained from the patient to participate in research.

Measurement of Outcome

Severity of symptoms of depression, mania, and ADHD were assessed weekly or bimonthly in the first 16 weeks and then every few months thereafter by a clinical psychologist using the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) Scales.[29] The CGI-S and CGI-I were assessed separately for depression, mania, and ADHD symptoms. The score for the CGI-S ranges from 1 (normal, not ill) to 7 (among the most extremely ill patients). The score for the CGI-I ranges from 1 (very much improved) to 7 (very much worse). The psychologist also used the Global Assessment of Functioning[30] (GAF), a numeric scale (1–100) used by mental health clinicians and doctors to rate the general functioning of adults; the Young Mania Rating Scale[31] (YMRS), an 11 item scale administered by a trained clinician who assigns a severity rating for each item based on a personal interview; and the Montgomery-Asberg Depression Rating Scale[32] (MADRS), a 10 item scale administered by a trained clinician who assigns a severity rating for each item of depression based on a personal interview.

Self-report and observer measures were also used to assess KT's mental symptoms. The Outcome Questionnaire[33] (OQ) is a 64 item measure of treatment progress for adults receiving mental health intervention. It involves three subscales: intrapersonal distress, interpersonal relations, and social problems. The OQ allows the clinician to compare the individual's behavior during treatment to normed samples of inpatient populations, outpatient populations, and a large untreated community population. A score of 63 is typically used as a cutoff for identifying individuals at high risk for psychiatric problems. The Conners' Adult ADHD Rating Scales[34] (CAARS) was used to assess *Diagnostic and Statistical*

Manual of Mental Disorders, Fourth Edition inattention, hyperactivity/impulsivity, and combined ADHD symptoms as well emotional lability. All raw scores can be converted to T-scores based on age and sex. The scale consists of a self-rating form and an observer form that is completed by an observer familiar with the adult's behaviors. In this case, KT's boyfriend, who lives with her, completed the form and was asked to reflect on KT's behavior over the last month.

Baseline haematological and biochemistry screening including: thyroid function, serum lipids, prolactin and glucose, blood clotting, iron, magnesium and copper levels, and urinalysis was completed. Other than her copper level (which fell below recommended levels), all results were within recommended levels. A neurocognitive assessment was also carried out at baseline and 1 year following the end of the open-label trial. It included subtests of the Wechsler Adult Intelligence Scale[35] (WAIS-III), the Wide Range Assessment of Memory and Learning[36] (WRAML-II), and the Wide Range Achievement Test[37] (WRAT-III). The Conners Continuous Performance Task[38] (CPT-II) was administered as a measure of impulsivity and inattention.

Baseline Prior to the Nutritional Intervention

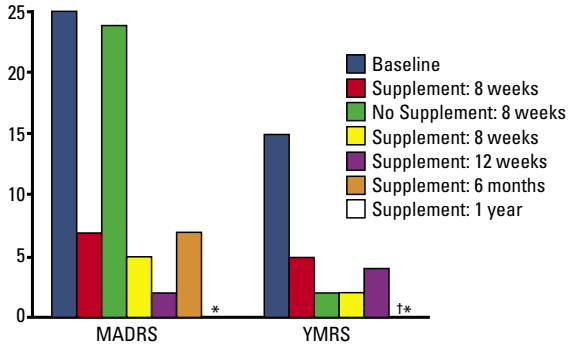
Based on the Structured Clinical Interview for *DSM-IV* axis I disorders[39] and the Conners' Adult ADHD Diagnostic Interview for *DSM-IV,*[40] at 20 years of age, KT met *DSM-IV* criteria for ADHD combined type, bipolar II disorder, social phobia, and panic disorder with agoraphobia. Her clinician-rated depression, as measured by the MADRS, was 25 (moderate severity range). KT entered the trial in a depressed episode that had been present for 2 years with intermittent hypomanic symptoms. Her score on the YMRS (15) was consistent with this low mood, the score reflecting the presence of ADHD symptoms rather than heightened mood symptoms. She obtained a CGI-S of moderately ill for both depression and ADHD. The CAARS self-rating and observer measures indicated clinical elevations on measures of emotional lability, inattention, and hyperactivity/impulsivity (T-scores >65). KT reported significant behavioral and psychiatric concerns as reflected by her OQ score of 76. Her GAF score was 45, indicative of serious symptoms and serious impairment in functioning. Figures 1 and 2 illustrate KT's baseline symptoms, indicating she was experiencing clinically elevated scores in mood lability, depression, and ADHD symptoms.

First Intervention with EMP+

KT began the micronutrient formula at 5 capsules/day divided into three doses and titrated up over a 1 week period to the full dose of 15 capsules/day divided into three equal doses, taken with food and plenty of water. The formula consists of large gelatin capsules of a similar size to an adult multivitamin. Only minor side effects were reported, such as a mild headache and mouth ulcer, but these were transient and only occurred in the first couple of weeks. KT's compliance was excellent in that she took the full dose of 15 capsules/day (based on number of pills dispensed and returned). KT was followed every week for an 8 week period. Although there was little change in the first 2 weeks (her MADRS scores stayed in the moderate range), by 3 weeks, there were noticeable changes in KT's symptoms. Her mood had lifted substantially, confirmed by a MADRS score of 6 (in remission). She reported being less irritable, more motivated, and more interested in life.

All outcome measures were repeated at 8 weeks (Figures 1 and 2). Depression was reduced substantially, confirmed by a MADRS rating of 7 (in remission). This represented a 72% reduction in her depression score from baseline. KT's CGI-S ratings for depression and ADHD were normal/not ill and minimally ill, respectively. Her CGI-I ratings for depression and ADHD were very much improved and much improved, respectively. Self-report CAARS scores confirmed changes in that there was substantial improvement from baseline on measures of emotional lability, hyperac-

FIGURE 1.
MADRS and YMRS scores across time and formula use



* Score was 0 at 1 year. † Score was 0 at 6 months.

MADRS=Montgomery-Asberg Depression Rating Scale; YMRS=Young Mania Rating Scale.

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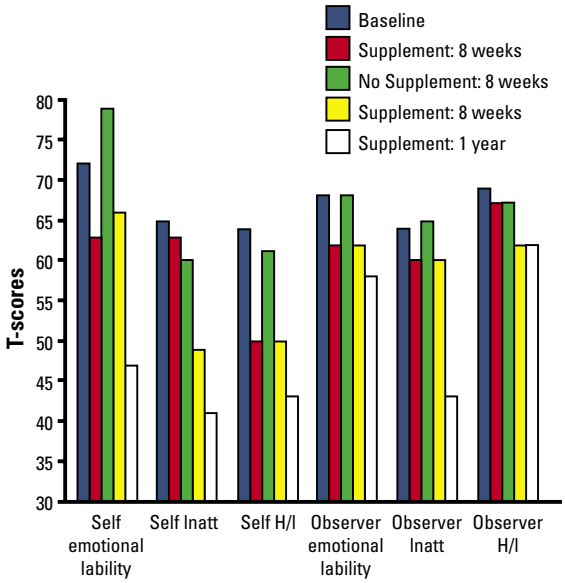
tivity, and impulsivity. Changes, while present, were more modest based on the observer report. Interestingly, little change was observed in the inattention subscale, consistent with patient report. Self-reported behavioral difficulties, as measured by the OQ, reduced to a score within a range found in community samples. Her GAF score of 75 shows a substantial improvement in overall functioning, indicative of mild symptoms. Her blood and urine tests were repeated and there were no changes from baseline.

After 8 weeks on the formula, KT decided to come off EMP+ because she believed her improvements in mood were due to contact with the primary investigator. She consented to be monitored during this phase.

Treatment Withdrawal

Two weeks after the treatment was discontinued, KT already reported being more irritable and hyperactive, and at 4 weeks she was more "blunt, snappy, and grumpy". Two months after stopping EMP+, KT reported low mood, a lack of motivation, tearfulness, and irritability towards her mother and her boyfriend. She experienced substantial difficulties in starting simple routine activities. KT reported that her co-workers noticed she was more talkative/outspoken since she had come off EMP+. Outcome measures were repeated at 8 weeks off EMP+ (Figures 1 and 2). Her depression symptoms returned to baseline severity level, confirmed by a MADRS rating of 24 (moderate severity). Her CGI-S ratings for depression and ADHD both returned to baseline levels (moderately ill). Most notably, self-reported and observer-reported emotional lability/impulsivity returned to baseline levels (self-reported symptoms were even higher than baseline), as well as self-reported hyperactivity/impulsivity. Her OQ score increased to 51. Overall functioning also deteriorated, reflected by a GAF score of 60. KT concluded that she was going to end up "ruining her life" and decided to resume EMP+.

FIGURE 2.
CAARS scores for both self and observer across time and formula use



CAARS=Conners Adult ADHD Rating Scale; Inatt=DSM-IV inattention; H/I=DSM-IV hyperactivity/impulsivity.

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Reintroduction of EMP+

KT was seen every few months to 1 year. Outcome measures were repeated at 8 weeks and 12 months back on EMP+ (Figures 1 and 2). At 8 weeks back on, improvement was noted in all areas of functioning. At 12 months back on EMP+, KT was in remission of all mental illness. Remission of depression was confirmed by a MADRS score of 0 and psychiatric interview. Her CGI-S ratings for depression and ADHD were both normal, not ill, and CGI-I ratings were both very much improved since the worst phase. On the CAARS, all scores were now in the nonclinical range. Self-rated and observer-rated inattention showed reductions from baseline of 37% and 33%, respectively, which represent changes of greater than 2 standard deviations (SD). Self-rated and observer-rated hyperactivity/impulsivity showed reductions from baseline of 33% (2 SD) and 10% (.5 SD), respectively. Her OQ score (22) was the lowest it had been and her overall functioning was also the highest (GAF=90).

KT did not become hypomanic at any point during this follow-up phase. Her highest score on the YMRS was 15 (baseline). She also reported better health (getting sick less often and that her glands were less swollen, an ongoing problem since having glandular fever in high school). She had successfully quit smoking for 9 months. Interestingly, about 6 weeks after she resumed EMP+ she took an antibiotic for an infection. She found her psychiatric symptoms worsened during the 10 day course of the antibiotic but were again well controlled once she stopped the antibiotic.

Neurocognitive Changes

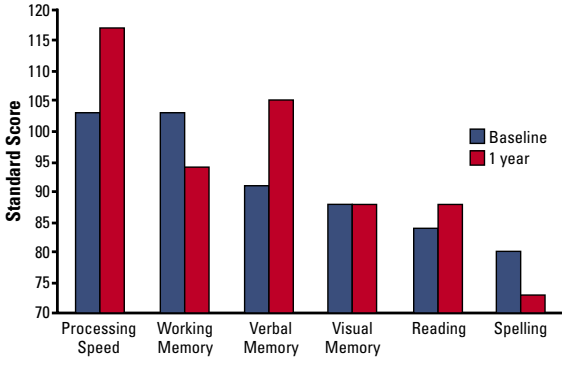
KT's cognitive functioning was assessed at baseline and then again 1 year following the end of the open-label trial (Figure 3). Alongside her

behavioral changes, neurocognitive changes were also found. There was an increase of almost 1 SD on the processing speed index of the WAIS-III (from a standard score [SS] of 103 at baseline to 117 at 1 year follow-up). The change was entirely driven by improvement in her performance on the coding subtest, a test that measures speed and accuracy of visual-motor coordination, speed of mental operation, attentional skills, and short-term memory for new learning. Her SS on this subtest went from average (50th percentile) to high average (84th percentile), suggesting that KT processes and retains new information more easily than she did on the previous testing session.

There was also an increase of almost 1 SD on the verbal memory index of the WRAML-II (from an SS of 91 at baseline to 105 at follow-up); however, visual memory did not change (remained at an SS of 88). Working memory dropped somewhat from baseline to one-year follow up (SS of 103 at baseline to 94 at follow-up) but these scores are comparable based on confidence index scores. Not surprisingly, there was none or little change in her WRAT-III scores on reading and spelling.

Her CPT changes were variable. KT showed a 1 SD improvement from baseline to 1 year follow-up on a measure of her variability of responses, her score improving from the 54th to 21st percentile, indicating greater consistency in response speed. She also showed a >1 SD improvement from baseline to follow-up in her hit reaction time, improving from the 81st percentile to the 31st percentile, indicating improved vigilance/sustaining reaction time. However, there was no change in her omissions (45th percentile) and she had more commission errors at follow-up compared with baseline showing a 1 SD change (28th percentile to 79th percentile).

FIGURE 3.
Neurocognitive function at baseline and after 1 year on formula



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DISCUSSION

KT is a 21-year-old with bipolar disorder II and ADHD who responded to a micronutrient formula (EMP+), with improvements in all her psychiatric symptoms including anxiety, depression, and ADHD. The treatment response was replicated through an ABAB design, showing on-off control of symptoms with the micronutrients. After 1 year she showed further gains and was in remission of all psychiatric conditions. Of notable clinical interest, no long-term side effects were reported while on EMP+. Perhaps more remarkably, KT achieved these changes after a long and well documented history of poor response to conventional treatments. However, more importantly, one intervention stabilized both ADHD and mood symptoms as well as anxiety, a finding not typically reported in the psychopharmacological literature.

KT's symptoms of hyperactivity and impulsivity, at least according to self-report, changed more rapidly as compared with her symptoms of inattention, consistent with the results of the larger open-label trial with adults with ADHD and mood dysregulation.[28] This study found that while inattention improved after 8 weeks, the means continued to fall in the clinical range, whereas the improvement in the hyperactive/impulsive symptoms resulted in means that fell in the normal range. However, after 12 months on the formula, KT's inattention symptoms had now equally improved. This self-report change was also noted by the observer report (although not to the same extent) and supported by the clinician interview. It is possible that EMP+ is having a more direct impact on the neurochemical pathways involved in inhibition, impulsivity, hyperactivity, and mood regulation than inattention. However, perhaps as KT's mood improved, she was better able to develop strategies to assist with her inattention. Further research is required to identify the specific neurochemical changes that may be occurring to better understand the differential impact that EMP+ appears to have on the two dimensions of ADHD symptoms.

This improvement in attention at 1 year is consistent with the neurocognitive data in that KT showed a 1 SD change in the coding subtest over a year's testing, a subtest of the WAIS-III well documented to be impaired in individuals with ADHD.[41] This change is reliable in that it is

more than one would expect given the standard error of measurement of the index. It is interesting to note the lack of change in working memory; however, research has found that working memory deficits are more attributable to reading difficulties than ADHD.[41] Given KT's long standing history of problems with reading and continued problems as noted in the neurocognitive testing of reading and spelling, it is perhaps not surprising that she did not show improvement in her working memory.

The changes on the CPT also confirmed the behavioral changes noted. Variability on the CPT has been one of the most consistently reported problems in ADHD[41-43] and has been identified as a better marker for ADHD than scores on omissions and commissions.[44] That KT showed a substantial improvement on this score is consistent with her reported improvements in her ADHD ratings on the CAARS. Further, the changes noted on the CPT are similar to ones found when individuals are tested on and off methylphenidate.[45] Although her commission score did get worse after 1 year, it was still within a normal nonclinical range. While it is difficult to identify neurocognitive tests that are specific to mood problems, it has been fairly consistently noted that individuals with bipolar disorder have impaired verbal memory.[46] Consistent with the improved mood changes, KT's verbal memory also improved by 1 SD, again a reliable change.

It is important that these neurocognitive changes be interpreted cautiously given that practice effects and standard error of measurement can explain changes from one testing period to another, although practice effects are less likely with such a long gap (1 year) between testing sessions. However, the fact that no test result became substantially worse from baseline to the final testing is important given that some medications used to treat mood problems may cause cognitive deficits.[47] Further, the lack of change in some tests (such as visual memory) suggests that the changes observed were not simply due to practice.

Kaplan and colleagues[19] hypothesize that unstable mood may be a manifestation of inborn metabolism errors which can have many effects on enzymatic reactions and ultimately brain function. Micronutrients are involved in enzymatic reactions that are responsible for the synthesis and metabolism of neurotransmitters.[27] Deficiencies in these essential cofactors would lead to depletions in the essential neurotransmitters required for optimal functioning. Certainly many nutrients contained in EMP+ have been identified as deficient/low in some people with depression (eg, vitamin B9, vitamin B12, vitamin B6, vitamin E, calcium, iron, magnesium, zinc[19]) and ADHD (eg, zinc,[48] magnesium[49]). It is possible that this intervention normalized any nutritional deficiency or impaired ability to utilize nutrients that may have been contributing to KT's psychiatric symptoms. Indeed, the fact that the use of an antibiotic resulted in a re-emergence of psychiatric symptoms lends some support to the idea that nutritional deficiencies may at least in part be contributing to KT's presentation. Although the direct effect of antibiotics on specific nutrient absorption is very difficult to assess, some research suggests that antibiotics can impair the body's ability to absorb nutrients by changing the gut flora involved in their digestion and absorption.[50-52]

There is also an emerging literature investigating the role that mitochondria play in psychiatric illnesses. Recent studies suggest that the manufacture of adenosine triphosphate, the energy source of the mitochondria, is compromised in bipolar disorder, ADHD, and other mental disorders.[53-55] Although still in its infancy, there is a growing body of literature suggesting that micronutrients can be used to treat mitochondrial diseases[56] and as such, one possible mechanism of action of EMP+ is by increasing mitochondrial energy metabolism.

Individual contact with the investigators is unlikely to explain the dramatic changes in KT's symptoms as this contact was gradually tapered off over time and contact over the last 9 months, when the symptoms were in remission, was negligible. Contact with the investigators occurred even when KT was not taking the micronutrients, indicating that contact alone cannot explain presence or absence of symptoms. Placebo response cannot be dismissed; however, there are several reasons it is unlikely. First, there was no therapeutic benefit until 3 weeks after beginning the micronutrients. Second, KT chose to come off the treatment because she thought her symptom improvement was due to contact and care received as part of a trial. Third, the changes have been maintained for a long period of time (1 year) and placebo effects are not likely to last for this long. Indeed, her symptoms continued to show improvement over an extended period of time. It is possible that KT changed her diet as a consequence of her involvement in this trial; however, as her diet was not adequately assessed, we cannot determine the extent that such changes may have influenced the outcome.

CONCLUSION

This case study is consistent with the growing positive findings using EMP+ for the treatment of various psychiatric conditions[20,21,24-26,28,57] and also extends the literature on EMP+ as it documents neurocognitive changes occurring in conjunction with the behavioral changes. These consistently positive outcomes alongside an absence of side effects indicate that further research, particularly larger and more controlled trials, is warranted using this multinutrient approach. ***CNS***

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