

## **Research Proposal**

# ***Orthomolecular Medicine Treatment of Bipolar Disorder***

Charles Gant MD, PhD, NMD

### **Summary of Project**

The goal of this 4-month, outcome-based trial is to evaluate the efficacy of an orthomolecular medicine<sup>1</sup> intervention in the treatment of Bipolar Disorder. Forty (40) patients will be screened by psychiatric evaluation and be determined to meet the criteria for Bipolar Disorder as defined by the DSM IV<sup>2</sup> and will be evaluated by psychological testing instruments. The subjects will be further evaluated by laboratory (physiological) tests (hair, blood and stool) to determine various physiological abnormalities that studies suggest are associated with Bipolar Disorder (e.g., amino acid deficiencies, heavy metal toxicity). Targeted nutritional supplementation based on the physiological abnormalities discovered on laboratory testing will be used as the primary treatment intervention. The subjects will be followed closely with standard psychiatric care. At four months they will be reevaluated by psychiatric examination, by psychological testing and laboratory testing to determine treatment outcomes.

### **Research Findings from Two Harvard Medical School Affiliated Studies**

Attached are articles authored by Dr. Charles Popper<sup>3</sup> and by Dr. Andrew Stoll (et. al.).<sup>4</sup> This research suggests that physiological abnormalities in mineral, B vitamin and omega-3 fatty acid metabolism are common enough in patients with Bipolar Disorder, that uniform treatment with these agents is able to achieve positive clinical outcomes. The purpose of this proposed study would be to ascertain beforehand what the unique physiological deficits are in each patient with Bipolar Disorder for these and other physiological parameters, and to target specific interventions based on that information.

### **Significance of the Study**

Starfield<sup>5</sup> suggested that iatrogenic causes of death in the US constitute the third leading cause of death, after deaths from heart disease and cancer. Most of the morbidity and mortality in these calculations stemmed from prescription medication. Posner<sup>6</sup> found that mortality increases many times in those patients who mix illicit drugs and/or alcohol with prescription medication. If nutritional supplements were to proven to be as effective as prescription drugs for the treatment of Bipolar Disorder and were eventually used as the primary method of treatment, there would be marked improvements in morbidity and mortality statistics for this disorder. Also, there are few if any minor side effects from nutritional supplementation and there are no concerns for long term use.

### **Expedited Approval**

Expedited approval from the IRB is requested because the intervention being tested has no known negative effects on patients.

### **Background**

The DSM IV<sup>7</sup> (Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition) characterizes two main types of Mood Disorders, Depressive Disorders and Bipolar Disorders. These categories are further delineated in various categories (e.g., Major Depressive Disorder,

Bipolar I Disorder, Bipolar II Disorder). The DSM IV explicitly defines the meaning of the term disorder.<sup>8</sup>

*In DSM-IV, each of the mental disorders is conceptualized as a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress (e.g., a painful symptom) or disability (i.e., impairment in one or more important areas of functioning)...*

*...Whatever its original cause, it must currently be considered a manifestation of a behavioral, psychological, or biological dysfunction in the individual...*

*In DSM-IV, there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder. There is also no assumption that all individuals described as having the same mental disorder are alike in all important ways. The clinician using the DSM-IV should therefore consider that individuals sharing a diagnosis are likely to be heterogeneous<sup>9</sup> even in regard to the defining features of the diagnosis and that boundary cases will be difficult to diagnose in any but a probabilistic fashion.*

Thus, while individuals diagnosed with a specific Mood Disorder may share a similar range of outward behavioral symptoms, the underlying causalities are “likely to be heterogeneous<sup>10</sup>,” “composed of unlike substances<sup>11</sup>,” “consisting of dissimilar elements<sup>12</sup>” and “completely different<sup>13</sup>.” Such heterogeneity could be within biological, psychological and/or social levels of organization<sup>14</sup> (The Biopsychosocial Model<sup>15</sup>) or could vary widely within each level of organization for each individual with a Mood Disorder.

At least at the biological level of the biopsychosocial model, a significant body of peer-reviewed literature strongly supports a heterogeneous molecular etiology for Mood Disorders, with each individual likely to have a unique array of abnormalities that *in toto* for each individual are expressed symptomatically as a Mood Disorder. Kaplan<sup>16</sup> and Popper<sup>17</sup> found that a proprietary blend of minerals and B vitamins was able to stabilize the mood of most bipolar patients. Stoll<sup>18</sup> conducted a double-blind, placebo-controlled study that demonstrated omega-3 fatty acids to be capable of significantly lengthening the period of remission for patients diagnosed with Bipolar Disorder. Domnisse<sup>19</sup> found that even borderline low normal vitamin B12 levels were associated with various psychiatric disorders, including Bipolar Disorder. An excellent review of the relationship of a folic acid deficiency to depression was published by Alpert<sup>20</sup>, and Fava<sup>21</sup> found that patients with low folic acid levels were less likely to respond to fluoxetine. Birkmayer<sup>22</sup> found that 93% of patients with depression responded favorably to NADH (Vitamin B3 analogue), a cofactor for the conversion of tyrosine to noradrenalin and for the conversion of tryptophan to 5-hydroxy tryptophan (precursor to serotonin). Maes<sup>23</sup> discussed the relationship of low tryptophan levels in depression and found them to be related to a generalized disorder in protein metabolism. Fekkes<sup>24</sup> found abnormal levels of serine in patients with Bipolar Disorder. Vitamin B2 (Riboflavin) was determined by Bell<sup>25</sup> to have a possible association to unipolar depression in women. In a double-blind trial comparing 5-hydroxytryptophan to imipramine, Angst<sup>26</sup> showed that 5-hydroxytryptophan had equal efficacy to imipramine in the treatment of depression. Using the Hamilton Depression Scale, no significant differences were discovered by Beckmann<sup>27</sup> in a double-blind study comparing the effects of imipramine and DL-Phenylalanine in the treatment of depression.

In addition to the evidence suggesting that deficiencies of certain nutritional agents are related to Mood Disorders, various toxicity- and immune-related conditions have been found to be related to

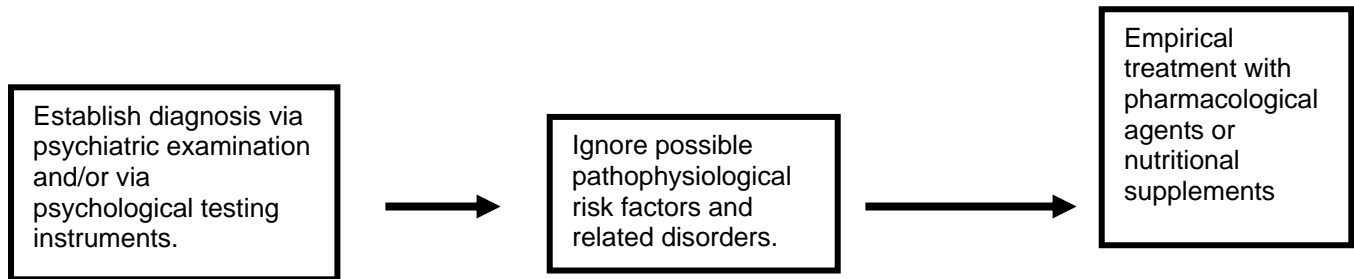
Mood Disorders. Hallert<sup>28</sup> found a relationship between Celiac Disease (wheat/gluten allergy) and depression. Siblingud<sup>29</sup> found a significant association between mercury amalgam removal and reversal of Bipolar Disorder symptoms. A strong association between iron toxicity and Bipolar Disorder was determined by Feifel<sup>30</sup>. Foulks<sup>31</sup> studied a group of patients who were at risk for exposure to toxic waste contamination and found that they reported higher levels of depression and anxiety.

These studies suggest etiological relationships between various nutritional deficiencies and toxicity/immune conditions and Bipolar Disorder. However, in most of the studies cited, there was little attempt to control for or search for a multiplicity of factors that could underlie the unique heterogeneous molecular causes of Mood Disorders in each patient. Obviously a wide variation of molecular heterogeneity exists in people suffering with Mood Disorders. Rather than designing a study that would empirically apply a single or uniform intervention to a group of subjects with a specific diagnosis of a Mood Disorder, as if they shared identical or similar biochemical abnormalities, the purpose of this proposed study would be instead to shift the paradigm to a whole new level. Since CLIA<sup>32</sup> certified medical laboratories now provide cost-effective, standardized testing panels that are routinely used to search for the unique abnormalities in individual patients, the precise and unique molecular heterogeneity of each patient can be diagnosed prior to treatment, and then a treatment plan can be designed that targets the specific abnormalities found (see Figure I below). The diagnostic panels for each patient would be those that more or less would be attempting to find abnormalities that studies such as those above had found to be related to Mood Disorders or more specifically various Bipolar Disorders.

# FIGURE I

## “USUAL AND CUSTOMARY” TREATMENT CONTRASTED WITH PROPOSED METHODOLOGY OF TREATMENT

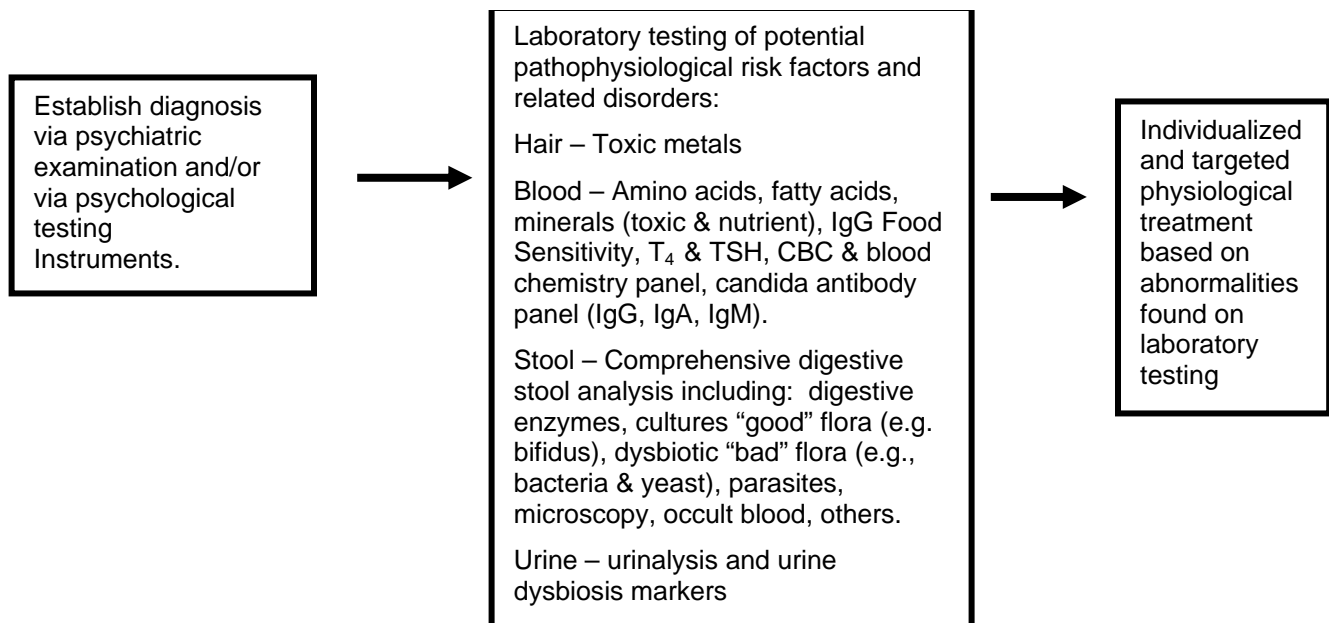
### The Usual and Customary Process



---

---

### PROPOSED TREATMENT PROCESS IN THIS STUDY



## **Hypothesis**

Based on the outcomes of studies presented above and our clinical experience, we hypothesize that interventions with nutritional supplements targeted to laboratory-determined physiological abnormalities will achieve positive clinical outcomes for Bipolar Disorder.

## **Outcome Measures**

At the beginning of the study and at the end of the study, the patients will be evaluated by an independent psychiatrist unfamiliar with the study parameters, the psychiatrist following the patient throughout the study and various psychological testing instruments as listed below.

- MMPI (The Minnesota Multiphasic Personality Inventory)
- Hamilton Depression Scale
- Changes in medication dosages<sup>33</sup>
- The Patient's Experience of Anxiety will be evaluated using Spielberger's rating scale, State-trait Anxiety Inventory (STAI) and the Visual Analog Scale (VAS).
- The Patient's Experience of Stress will be evaluated using the Perceived Stress Scale.
- The Patient's moods will be further evaluated using the Profile of Moods Scale.
- The patient's well-being will be measured using the SF-36.

Patients will be surveyed on their experiences with complementary medicine and alternative medicine interventions using a customized Complementary and Alternative Medicine<sup>34</sup> Survey.

Furthermore, at the conclusion of the study, retesting of the physiological, laboratory tests (see Figure I) will be done. Statistical analysis comparing the changes on psychiatric (independent psychiatric evaluation), psychological (test batteries) and physiological (laboratory testing) will be done.

## **FIGURE I**

### **Laboratory Tests to be Used in the Study to Determine the Underlying Physiological Abnormalities Possibly Associated with Bipolar Disorder**

- 1) SMAC (Labcorp)
- 2) CBC (Labcorp)
- 3) U/A (Labcorp)
- 4) T4, TSH (Labcorp)
- 5) Plasma Amino Acid Analysis (GSDL<sup>35</sup>)
- 6) RBC Minerals (GSDL)
- 7) EFA Testing (GSDL)
- 8) Food Allergy (Metamatrix<sup>36</sup>)
- 9) Candida protocol (GSDL)
- 10) Hair Testing (at Doctors Data)
- 11) Microbiology (GSDL)
- 12) Urine Dysbiosis Markers (Metamatrix)



## References and Footnotes

<sup>1</sup> Ortho means “to straighten or correct,” as in orthopedic interventions which straighten or correct the bones or orthodontic interventions which straighten or correct the teeth. Orthomolecular medicine is a term coined by Linus Pauling (<http://www.orst.edu/dept/lpi>), one of the 20th century’s greatest scientists and the only person to win two independent Nobel Prizes (Chemistry and Peace). In the process of “straightening out or correcting” (ortho) the molecules, harmful toxic substances (e.g., lead) that are found to be present in the body are removed and healthful nutrient substances (e.g., zinc) that are found to be missing from the body are restored.

<sup>2</sup> American Psychiatric Association Staff: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.

<sup>3</sup> Popper CW. Do Vitamins or Minerals (Apart From Lithium) Have Mood-Stabilizing Effects? *J Clin Psychiatry* 2001;62:12.

<sup>4</sup> Stoll AW, Severus WE, Freeman MP, et. al. Omega 3 Fatty Acids in Bipolar Disorder. *Archives of General Psychiatry* 1999;56:407-411.

<sup>5</sup> Starfield B. Is US Health Really the Best in the World? *JAMA*; July 26, 2000;284(4):483-485.

<sup>6</sup> Poser W et. al. Mortality in patients with dependence on prescription drugs. *Drugs and Alcohol Dependence* 1991;30:49-57.

<sup>7</sup> American Psychiatric Association Staff: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.

<sup>8</sup> *Ibid.*, pp. xxi – xxii.

<sup>9</sup> **Heterogeneous** (het-er-o-je’ne-us) [G. eteros, other, + gennos, type]. Of unlike natures composed of unlike substances. In contrast to homogeneous, q.v. (Taber’s Cyclopedic Medical Dictionary, 11th edition. Philadelphia: F.A. Davis Company; 1970).

**Heterogeneous 1.** Consisting of dissimilar elements or parts; not homogeneous. **2.** Completely different; incongruous (The American Heritage Dictionary, third edition. New York: Bantam Doubleday Dell Publishing Group; 1994).

<sup>10</sup> *Op. cit.*, The American Psychiatric Association, DSM-IV, p. xxii.

<sup>11</sup> *Op. cit.*, Taber’s Cyclopedic Medical Dictionary.

<sup>12</sup> *Op. cit.*, The American Heritage Dictionary.

<sup>13</sup> *Op. cit.*, The American Heritage Dictionary.

<sup>14</sup> Life condenses around different levels of organization according to the following scheme: atoms→ molecules→ macromolecules→ intracellular organelles→ cells→ tissues→ organs/organ systems→ person→ two person→ family→ community→ etc. (see reference below, Engle)

<sup>15</sup> Engle G. The clinical application of the biopsychosocial model. *Am J Psychiatry* 1980; 137(5):535-544

<sup>16</sup> Kaplan BJ, Simpson JSA, Ferre RC, et al. Effective mood stabilization with a chelated mineral supplement: an open-label trial in bipolar disorder. *J Clin Psychiatry* 2001;62:936-944

- <sup>17</sup> Popper CW. Do Vitamins or Minerals (Apart From Lithium) Have Mood-Stabilizing Effects? *J Clin Psychiatry* 2001;62:12.
- <sup>18</sup> Stoll AW, Severus WE, Freeman MP, et. al. Omega 3 Fatty Acids in Bipolar Disorder. *Archives of General Psychiatry* 1999;56:407-411
- <sup>19</sup> Dommissie JV. Subtle Vitamin B12 Deficiency in Psychiatry: A Largely Unnoticed But Devastating Relationship? *Medical Hypothesis* 1991;34:131-140.
- <sup>20</sup> Alpert JA, Fava M. Nutrition and Depression: The Role of Folate. *Nutrition Reviews* 1997; 55(5):145-149.
- <sup>21</sup> Fava M, et. al. Folate, Vitamin B12, and Homocysteine in Major Depressive Disorder. *American Journal of Psychiatry* 1997;154:3:426-428.
- <sup>22</sup> Birkmayer JGD, Birkmayer W. The Coenzyme Nicotinamide Adenine Dinucleotide (NADH) as Biological Antidepressive Agent: Experience With 205 Patients. *Trends in Clinical Neuropharmacology* 1992;1-7.
- <sup>23</sup> Maes M, et.al. Lower Serum L-Tryptophan Availability in Depression as a Marker of a More Generalized Disorder in Protein Metabolism. *Neuropsychopharmacology* 1996;15(3):243-251.
- <sup>24</sup> Fekkes, Durk, et. al. Abnormal Plasma Levels of Serine, Methionine and Taurine in Transient, Acute, Polymorphic Psychosis. *Psychiatry Research* 1994;51:11-18.
- <sup>25</sup> Bell IR, et.al. Low Thyroxine Levels in Female Psychiatric Patients With Riboflavin (Vitamin B2) Deficiency: Implications For Folate Dependent Methylation. *ACTA Psychiatrica Scand* 1992;85:360-363.
- <sup>26</sup> Angst J, Woggon B, Schoepf J. The Treatment of Depression With L-5 Hydroxytryptophan Versus Imipramine. Results of Two Open and One Double-Blind Study. *Archives Psychiatr Nervenkr* 1977;224(2):175-186.
- <sup>27</sup> Beckmann H, Athen D, Olteanu M, Zimmer R. DL-Phenylalanine Versus Imipramine: A Double-Blind Controlled Study. *Archives Psychiatr Nervenkr* 1979;227(1):49-58.
- <sup>28</sup> Hallert C. Depression in Coeliac Disease. *Epilepsy and Other Neurological Disorders in Coeliac Disease* 1997;28:211-217.
- <sup>29</sup> Siblingrud RI, et. al. Psychometric Evidence That Dental Amalgam Mercury May Be an Etiological Factor in Manic Depression. *Journal of Orthomolecular Medicine* 1998;13(1):31-41.
- <sup>30</sup> Feifel D, Young CW. Iron Overload Among a Psychiatric Outpatient Population. *Journal of Clinical Psychiatry* 1997;58(2):74-78.
- <sup>31</sup> Foulks E, McClellan T. Psychologic Sequelae of Chronic Toxic Waste Exposure. *Southern Medical Journal* 1992;85(2):122-126.
- <sup>32</sup> CLIA stands for the Clinical Laboratory Improvement Act of 1988 (Federal). HICFA is the enforcement arm of the Act. CLIA certification means that certain federal guidelines for quality assurance and staff training must be met. CLIA certification is the standard certification for all medical laboratories in the US.
- <sup>33</sup> Depending on patient responses, the requirements for medication will be assessed and reassessed on an ongoing basis.

<sup>34</sup> The home page of the White House Commission on Complementary and Alternative Medicine Policy, WHCCAMP, at [WHCCAMP@mail.nih.gov](mailto:WHCCAMP@mail.nih.gov), or contact them at 6707 Democracy Boulevard, Room 880, MS – 5467, Bethesda, Maryland 20892 TEL: 301-435-7592, FAX: 301-480-1691

<sup>35</sup> GSDL is an abbreviation for Great Smokies Diagnostic Laboratory, a CLIA certified laboratory in Asheville, NC. They can be contacted at [www.GSDL.com](http://www.GSDL.com) or at 800-52-4762.

<sup>36</sup> Metametrix is a CLIA certified medical laboratory in Norcross, Ga. They can be reached at 800-221-4640 or at [www.metametrix.com](http://www.metametrix.com).