How Do Orthomolecules Work? A Pragmatic Perspective Based on their Presumed Psychoactive Effects

Jonathan E. Prousky, ND, MSc, MA[1,2]

[1] Chief Naturopathic Medical Officer, Professor, Canadian College of Naturopathic Medicine, 1255 Sheppard Avenue East, Toronto, Ontario, M2K 1E2, Tel: 416-498-1255 ext. 235, email: jprousky@ccnm.edu
[2] Editor, Journal of Orthomolecular Medicine, email: editor@orthomed.org

Abstract *The author presents the perspective that orthomolecular treatments possess psychoactive effects that result in potentially desirable physiological changes (e.g., sedation, psychomotor slowing, activation, and/or altered sense perception). The psychoactive effects of a broad range of commonly-recommended orthomolecular interventions are listed. This perspective can be integrated into a more expansive understanding of how orthomolecular interventions work, without claiming specific biochemical alterations. Lastly, several key advantages are delineated to support the use of orthomolecular interventions for their psychoactive effects.*

Introduction

Psychiatric medications are promoted as disease-modifying agents that treat mental disorders based on claims that they correct abnormal brain states by having some impact on underlying disease processes (Moncrieff & Cohen, 2009). Depressed patients, for example, are routinely offered psychiatric medication as a means to correct some abnormal brain state (i.e., serotonin deficiency), as a result of the drug's alleged action upon the underlying disease process (i.e., increasing serotonin to restore balance to an "imbalanced" central nervous system). However, the evidence, linking mental disorders to deficiencies or excesses of specific neurochemicals is devastatingly inadequate (Whitaker, 2005). Proof is lacking for some of the major theories of mental illness, such as the monoamine hypothesis of depression (Moncrieff & Cohen, 2006), and the dopamine hypothesis of schizophrenia (Moncrieff, 2009).

Just because a psychiatric medication moderates a patient's symptoms of psychosis or depression does not necessarily mean that the medication is correcting some underlying biochemical imbalance. On the contrary, psychiatric medications are more accurately understood as agents that induce an altered physical and mental state (Moncrieff & Cohen, 2009). The psychoactive effects are thus derived from the medication-induced alteration of brain activity. Alcohol is a good example that explains this medication-centred model of therapeutic effect. Some socially-anxious people feel less inhibited when they have a few drinks at public events. The alcohol is not correcting some brain imbalance, but rather is having a psychoactive effect by altering the brain in a manner that leads to less social inhibition.

From this perspective, it might be very desirable for patients with depression to feel stimulated after taking antidepressant medication if they then have more energy and motivation to participate in activities

that they had previously neglected (Moncrieff & Cohen, 2006). Similarly, antipsychotic medications as neuroleptic agents suppress central nervous system activity, give rise to neurological symptoms of Parkinsonism, and induce a state of indifference to one's surroundings and environment (Moncrieff, 2013). Through the suppression of central nervous system functioning, some patients with psychosis experience subjective benefits by becoming indifferent to symptoms of psychosis, such as auditory and/or visual hallucinations.

I believe that this medication-centred model can be integrated into a more expansive understanding of how orthomolecular interventions work. While it is customary for orthomolecularly-minded clinicians to ascribe clinical improvements to biochemical alterations, it would also seem reasonable to ascribe clinical improvements to the psychoactive effects resulting from altered mental states. For instance, the sedating effects of niacinamide might be desirable when alleviating agitation that can often accompany states of mental distress. This perspective embraces the concept that orthomolecular interventions possess psychoactive effects (without knowing the specific biochemical effects upon the brain and/or body), but based on clinical evidence that those psychoactive effects include desirable physiological changes (e.g., sedation, psychomotor slowing, activation, and/or altered sense perception).

In the subsequent sections of this paper, I will discuss the psychoactive benefits from commonly-recommended orthomolecular interventions. To illuminate the psychoactive effects of orthomolecular interventions, I will base the forthcoming information on my clinical experience and published studies. In this way, a model of orthomolecular therapeutic action encourages using these naturally-occurring molecules to alleviate mental distress because of their psychoactive effects as opposed to their ability to correct specific biochemical abnormalities. I will conclude by making the recommendation that orthomolecularly-minded clinicians should, as part of informed consent, let patients know that orthomolecular treatments possess a multitude of psychoactive effects that may be beneficial, without claiming specific biochemical alterations.

Psychoactive Effects of Commonly Recommended Orthomolecular Interventions

To base orthomolecular treatments on their psychoactive effects requires some explanation of the different psychoactive effects induced by these naturally-occurring molecules. From my perspective, the psychoactive effects of orthomolecular interventions can be broadly delineated into the following categories:

1. Activation (i.e., any orthomolecule, or combination thereof, which increases positive affect or reduces depression, stimulates, energizes, and/or increases motivation);
2. Altered sense perception (i.e., any orthomolecule, or combination thereof, which reduces symptoms of psychosis and/or that favourably alters how an individual responds internally and to others about prior misperceptions of reality);
3. Decreased reward-seeking behavior (i.e., any orthomolecule, or combination thereof, which decreases ruminative or obsessive thinking, the desire to use substances of abuse, and/or compulsive behaviour);
4. Enhanced cognition (i.e., any orthomolecule, or combination thereof, which increases the ability to maintain focus and attention, memory, and/or the speed of cognitive processing);
5. Psychomotor slowing (i.e., any orthomolecule, or combination thereof, which results in less akathisia, hyperkinetic activity, dyskinesia, dystonia, mania, hypomania, and/or less needless or incessant moving about); and
6. Sedation (i.e., any orthomolecule, or combination thereof, which produces a calming effect, and/or lessening of anxiety or "stress").

Below, I've listed the orthomolecules that I routinely use in clinical practice. The references (i.e., the most recent publications are listed first) were chosen based on evidence linking the particular orthomolecule to a well-delineated therapeutic effect that

could associate or "fit" within one or more of the categories described above. The included references were not scrutinized from a "best quality of evidence" perspective, but more from showing that a particular orthomolecule possesses a psychoactive effect, or range of psychoactive effects. It should be noted that the mere possessing of a psychoactive effect does not necessarily mean that the particular orthomolecule will result in a significant clinical effect or benefit for every patient who has the same diagnosis.

Purported Psychoactive Effects of Selected Orthomolecules (in alphabetical order)

5-hydroxytryptophan (5-HTP)
Activation: Jangid, Malik, Singh, & Sharma, 2013; Meyers, 2000; Birdsall, 1998
Sedation: Kahn & Westenberg, 1985
Suggested daily dose: 50-3,250 mg

5-Methyltetrahydrofolate (5-MTHF)
Activation: Miller, 2008; Guaraldi, Fava, Mazzi, & la Greca, 1993
Suggested daily dose: 15-50 mg

Acetyl-L-Carnitine (ALC)
Activation: Malaguarnera et al, 2008; Zanardi & Smeraldi, 2006; Montgomery, Thal, & Amrein, 2003; Pettegrew et al, 2002; Garzya et al, 1989; Tempesta et al, 1986
Enhanced cognition: Malaguarnera et al, 2008; Montgomery, et al, 2003; Spagnoli et al, 1991
Suggested daily dose: 1,500-4,000 mg

Alpha-tocopherol
Enhanced cognition: Kontush & Schekatolina, 2004
Psychomotor slowing: Adler et al, 1998; Barak, Swartz, Shamir, Stein, & Weizman, 1998; Junker, Steigleider, & Gattaz, 1992; Lohr et al, 1988
Suggested daily dose: 400-2,000 IU

Arginine
Sedation: Smirga et al, 2007; Daniela, Aikaterini, Miro, Yasushi, & Roman, 2005
Suggested daily dose: 2,640-3,000 mg

Ascorbic Acid
Activation: Amr, El-Mogy, Shams, Vieira, & Lakhan, 2013
Altered sense perception: Dakhale, Khanzode, Khanzode, & Saoji, 2005
Sedation: de Oliveira, de Souza, Motta, & Da-Silva, 2015; Mazloom, Ekramzadeh, & Hejazi, 2013; Stough et al, 2011; Kennedy et al, 2010; Brody, Preut, Schommer, & Schürmeyer, 2002
Suggested daily dose: 250-3,000 mg

B-Complex Vitamins
Activation: Lewis et al, 2013
Altered sense perception: Levine et al, 2006
Sedation: Stough et al, 2011; Kennedy et al, 2010
Suggested daily dose: 1 pill with doses of B-complex vitamins ranging from 10-100 mg with lesser (i.e., microgram) amounts of folic acid and cobalamin

Calcium
Activation: Harrison-Hohner et al, 2001; Thys-Jacobs, 2000; Ward & Holimon, 1999; Arasteh, 1994
Suggested daily dose: 1,000-2,000 mg (females)

Citicoline
Decreased reward-seeking behavior: Brown, Gorman, & Hynan, 2007
Enhanced cognition: Cotroneo et al, 2013; García-Cobos, Frank-García, Gutiérrez-Fernández, & Díez-Tejedor, 2010; Brown, Gorman, & Hynan, 2007; Alvarez et al, 1999
Suggested daily dose: 1,000-1,200 mg

Cobalamin
Activation: Mitchell, 2007; Yamada, 1995; Newbold, 1989; Ellis & Nasser, 1973
Enhanced cognition: van Tiggelen, Peperkamp, & Tertoolen, 1984
Suggested daily dose: 5,000-9,000 mcg intramuscularly (as hydroxocobalamin); 1,000-1,500 mcg orally (as methylcobalamin)

Coenzyme Q10 (COQ10)
Activation: Forester et al, 2012
Suggested daily dose: 1,200 mg

Cholecalciferol
Activation: Shaffer et al, 2014; Khoraminya, Tehrani-Doost, Jazayeri, Hosseini, & Djazayery, 2013; Shipowick, Moore, Corbett, & Bindler, 2009; Jorde, Sneve, Figenschau, Svartberg, & Waterloo, 2008
Suggested daily dose: 1,500-5,000 IU or 20,000-40,000 IU weekly

Choline bitartrate
Enhanced cognition: Fovall et al, 1980
Psychomotor slowing: Stoll, 1996
Suggested daily dose: 3-8 g (as free choline derived from choline bitartrate)

Creatine
Activation: Lyoo et al, 2012; Roitman, Green, Osher, Karni, & Levine, 2007; Amital, Vishne, Rubinow, & Levine, 2006; Amital, Vishne, Roitman, Kotler, & Levine, 2006
Enhanced cognition: Rae, Digney, McEwan, & Bates, 2003
Sedation: Amital, Vishne, Roitman, Kotler, & Levine, 2006
Suggested daily dose: 5,000 mg

Chromium
Activation: Docherty, Sack, Roffman, Finch, & Komorowski, 2005; Davidson, Abraham, Connor, & McLeod, 2003; McLeod & Golden, 2000; McLeod & Golden, 1999
Enhanced cognition: Krikorian, Eliassen, Boespflug, Nash, & Shidler, 2010
Suggested daily dose: 400-1,000 mcg

Dimethylaminoethanol (DMAE)
Activation: Coleman, Dexheimer, DiMascio, Redman, & Finnerty, 1976; Lewis & Young, 1975
Enhanced cognition: Coleman et al, 1976; Lewis & Young, 1975
Psychomotor slowing: Simpson, Voitashevsky, Young, & Lee, 1977; Coleman et al, 1976; Casey & Denney, 1975; De Silva & Huang, 1975; Fann, Sullivan, Miller, & McKenzie, 1975; Lewis & Young, 1975; Miller, 1974
Suggested daily dose: 300-1,200 mg

Folic acid
Activation: Mitchell, 2007; Abou-Saleh & Coppen, 2006; Coppen & Bailey, 2000 Suggested daily dose: 500-2,000 mcg

Gamma-aminobutyric acid (GABA)
Sedation: Yamatsu et al, 2015; Yoto et al, 2012; Abdou et al, 2006; Braverman, Pfeiffer, Blum, & Smayda, 1997
Suggested daily dose: 100-4,000 mg

Glutamine
Decreased reward-seeking behavior: Rogers & Pelton, 1957
Suggested daily dose: 2,000 mg

Glycine
Activation: Heresco-Levy, Ermilov, Lichtenberg, & Javitt, 2004; Heresco-Levy et al, 1999; Heresco-Levy et al, 1996; Javitt, Zylberman, Zukin, Heresco-Levy, & Lindenmayer et al, 1994
Decreased reward-seeking behavior: Cleveland, DeLaPaz, Fawwaz, & Challop, 2010; Greenberg et al, 2009
Suggested daily dose: 30-90 g (not to be combined with clozapine)

Inositol
Activation: Mukai, Kishi, Matsuda, & Iwata, 2014; Carlomagno, Unfer, Buffo, & D'Ambrosio, 2011; Nierenberg et al, 2006; Chengappa et al, 2000; Elizur, Kofman, & Belmaker, 1995
Decreased reward-seeking behavior: Gelber, Levine, & Belmaker, 2001; Fux, Benjamin, & Belmaker, 1999
Sedation: Palatnik, Frolov, Fux., & Benjamin, 2001; Benjamin et al, 1995
Suggested daily dose: 2-25 g

Inositol Hexaniacinate
Enhanced cognition: Loriaux, Deijen, Orlebeke, & De Swart, 1985
Suggested daily dose: 500 mg (providing a minimum of 140 mg of niacin)

Iron
Activation: Vaucher, Druais, Waldvogel, & Favrat, 2012 (women with serum ferritin < 50 ug/L and hemoglobin > 12.0 g/dL); McClung et al, 2009 (women); Verdon et al, 2003 (women with low or borderline serum ferritin

concentrations)
Enhanced cognition: Konofal et al, 2008 (non-anemic children with ferritin < 30 ug/L); Konofal, Cortese, Lecendreux, Arnulf, & Mouren, 2005 (non-anemic boy with low serum ferritin); Sever, Ashkenazi, Tyano, & Weizman, 1997 (non-anemic boys); Bruner, Joffe, Duggan, Casella, & Brandt, 1996 (adolescent girls with serum ferritin < 12 ug/L and normal hemoglobin)
Psychomotor slowing: Konofal et al, 2008 (non-anemic children with ferritin < 30 ug/L); Konofal, Cortese, Lecendreux, Arnulf, & Mouren, 2005 (non-anemic boy with low serum ferritin); Sever, Ashkenazi, Tyano, & Weizman, 1997 (non-anemic boys)
Suggested daily dose: 15-260 mg (elemental iron, females); 5 mg/kg or 80 mg (elemental iron, children)

Lysine
Activation: Zeinoddini et al, 2014
Altered sense perception: Zeinoddini et al, 2014; Wass et al, 2011
Enhanced cognition: Wass et al, 2011
Sedation: Smirga et al, 2007; Daniela, Aikaterini, Miro, Yasushi, & Roman, 2005
Suggested daily dose: 3,000-6,000 mg

Magnesium
Activation: Barragán-Rodríguez, Rodríguez-Morán, & Guerrero-Romero, 2008; Eby & Eby, 2006; Cox, Campbell, & Dowson, 1991; Facchinetti et al, 1991
Enhanced cognition: Mousain-Bosc et al, 2006; Starobrat-Hermelin & Kozielec, 1997
Psychomotor slowing: Mousain-Bosc et al, 2006; Starobrat-Hermelin & Kozielec, 1997
Sedation: De Souza, Walker, Robinson, & Bolland, 2000
Suggested daily dose: 200-1,200 mg (adults), or 6 mg/kg or 200 mg (children)

Manganese
Psychomotor slowing: Kunin, 1976
Suggested daily dose: 15-60 mg

Melatonin
Decreased reward-seeking behavior: Zhdanova & Piotrovskaya, 2000
Sedation: Ferracioli-Oda, Qawasmi, & Bloch, 2013; van Geijlswijk, Korzilius, & Smits, 2010; Brzezinski et al, 2005
Suggested daily dose: 0.1-10 mg

N-acetylcysteine (NAC)
Activation: Berk et al, 2011; Magalhães et al, 2011; Bulut et al 2009; Berk et al, 2008a; Berk et al, 2008b
Decreased reward-seeking behavior: Rodrigues-Barata, Tosti, Rodríguez-Pichardo, & Camacho-Martínez, 2013; Gray et al, 2012; Gray et al, 2010; Grant, Odlaug, & Kim, 2009; Mardikian, LaRowe, Hedden, Kalivas, & Malcolm, 2007; Lafleur, 2006; LaRowe et al, 2006
Psychomotor slowing: Berk et al, 2008b
Suggested daily dose: 1,200-3,600 mg

Nicotinamide adenine dinucleotide (NADH)
Activation: Birkmayer & Birkmayer, 1991
Enhanced cognition: Demarin, Podobnik, Storga-Tomic, & Kay, 2003; Birkmayer, 1996
Suggested daily dose: 5 mg

Niacin
Activation: Thompson & Proctor, 1953; Washburne, 1950
Altered sense perception: Hoffer, 1994; Osmond & Hoffer, 1962; Hoffer & Callbeck, 1962; Hoffer, Osmond, Callbeck, & Kahan, 1957; Gregory, 1952; Sydenstricker & Cleckley, 1941
Enhanced cognition: Hoffer, 1974; Hoffer, 1962; Gregory, 1952; Sydenstricker & Cleckley, 1941
Psychomotor slowing: Kunin, 1976
Sedation: Thompson & Proctor, 1953
Suggested daily dose: 75-4,500 mg

Niacinamide
Activation: Chouinard, Young, Annable, & Sourkes, 1979; Chouinard, Young, Annable, & Sourkes, 1977; MacSweeney, 1975
Altered sense perception: Hoffer, 1994; Hoffer, Osmond, Callbeck, & Kahan, 1957
Enhanced cognition: Brenner, 1982; Hoffer, 1971
Psychomotor slowing: Brenner, 1982; Hoffer, 1971
Sedation: Prousky, 2005; Prousky 2004; Wright, 1992

Suggested daily dose: 1,000-6,000 mg

Omega-3 essential fatty acids

Activation: Mocking et al, 2016; Sarris et al, 2016; Sarris, Mischoulon, & Schweitzer, 2012; Clayton et al, 2009

Enhanced cognition: Bloch & Qawasmi, 2011

Psychomotor slowing: Shakeri et al, 2016; Bloch & Qawasmi, 2011; Clayton et al, 2009

Sedation: Kiecolt-Glaser, Belury, Andridge, Malarkey, & Glaser, 2011; Buydens-Branchey, Branchey, & Hibbeln, 2008

Suggested daily dose: 360-4,400 mg EPA and 348-1,560 mg DHA

Phenylalanine

Activation: Birkmayer, Riederer, Linauer, & Knoll, 1984 (L-form); Beckmann, Strauss, & Ludolph, 1974 (D,L-form); Beckmann, Athen, Olteanu, & Zimmer, 1970 (D,L-form)

Decreased reward-seeking behavior: Blum, Trachtenberg, Elliot, Dingler, & Sexton, 1989 (equal amounts of the D- and L-forms); Blum & Trachtenberg, 1988 (equal amounts of the D- and L-forms); Blum, Allison, Trachtenberg, Williams, & Loeblich, 1988 (equal amounts of the D- and L-forms)

Suggested daily dose: 230-1,380 mg (L-form); 230-1,380 mg (D-form); 75-200 mg (D,L-form)

Phosphatidylserine

Activation: Maggioni et al, 1990

Enhanced cognition: Hirayama et al, 2014

Psychomotor slowing: Hirayama et al, 2014; Manor et al, 2012; Delwaide, Gyselynck; Mambourg, Hurlet, & Ylieff, 1986

Suggested daily dose: 150-300 mg

Pyridoxine

Activation: Kashanian, Mazinani, & Jalalmanesh, 2007; Wyatt, Dimmock, & Jones, 2000

Enhanced cognition: Dolina, Margalit, Malitsky, & Rabinkov, 2014; Mousain-Bosc et al, 2006; Brenner, 1982

Psychomotor slowing: Dolina, Margalit, Malitsky, & Rabinkov, 2014; Miodownik et al, 2006; Mousain-Bosc et al, 2006; Lerner, Kaptsan, Miodownik, & Kotler, 1999; Lerner & Liberman, 1998; Brenner, 1982

Sedation: Kashanian, Mazinani, & Jalalmanesh, 2007; Wyatt, Dimmock, & Jones, 2000

Suggested daily dose: 50-1,200 mg (adults); 0.6 mg/kg or up to 100 mg (children); 200 mg (adolescents)

S-adenosylmethionine (SAMe)

Activation: Sarris et al, 2016; Kagan, Sultzer, Rosenlicht, & Gerner, 1990; Bunney Jr, & Potkin, 1988

Suggested daily dose: 800-1,600 mg

Theanine

Enhanced cognition: Park et al, 2011

Sedation: Unno et al, 2013; Yoto, Motoki, Murao, & Yokogoshi, 2012; Lyon, Kapoor, & Juneja, 2011; Ristner et al, 2010; Nobre, Rao, & Owen, 2008; Lu et al, 2004; Juneja, Chu, Okubo, Nagato, & Yokogoshi, 1999

Suggested daily dose: 50-400 mg

Tyrosine

Activation: Neri et al, 1995; Mouret et al, 1988; Gelenberg, Wojcik, Gibson, & Wurtman, 1983; Gelenberg, Wojcik, Growdon, Sved, & Wurtman, 1980

Decreased reward-seeking behavior: Blum et al, 1988

Enhanced cognition: Mahoney, Castellani, Kramer, Young, & Lieberman, 2007; Deijen, Wientjes, Vullinghs, Cloin, & Langefeld, 1999; Neri et al, 1995; Deijen & Orlebeke, 1994; Shurtleff, Thomas, Schrot, Kowalski, & Harford, 1994; Reimherr, Wender, Wood, & Ward, 1987; Wood, Reimherr, & Wender, 1984

Psychomotor slowing: Reimherr, Wender, Wood, & Ward, 1987; Wood, Reimherr, & Wender, 1984

Sedation: Dollins, Krock, Storm, Wurtman, & Lieberman, 1995; Banderet & Lieberman, 1989

Suggested daily dose: 30-150 mg/kg

Tryptophan

Activation: Ghadirian, Murphy, & Gendron, 1998; McGrath, Buckwald, & Resnick, 1990;

Thomson et al, 1982; Chouinard, Young, Annable, & Sourkes, 1979; Chouinard, Young, Annable, & Sourkes, 1977; MacSweeney, 1975
Decreased reward-seeking behavior: Bowen, Spring, & Fox, 1991
Sedation: Schneider-Helmert & Spinweber, 1986
Suggested daily dose: 1-15 g

Zinc

Activation: Ranjbar et al, 2013; Lai et al, 2012; Siwek et al, 2009; Nowak, Siwek, Dudek, Ziêba, & Pilc, 2003
Enhanced cognition: Akhondzadeh, Mohammadi, & Khademi, 2004; Bilici et al, 2004
Psychomotor slowing: Akhondzadeh, Mohammadi, & Khademi, 2004; Bilici et al, 2004
Suggested daily dose: 15-30 mg

Discussion

There are several key advantages to clinicians and patients when orthomolecular interventions are recommended for their psychoactive effects. First, I believe this paradigm to be a more encouraging way to recommend orthomolecular interventions. I could never reasonably demonstrate to any patient that his/her clinical improvement was due to (or the result of), for example, a lowered homocysteine level, or raised serotonin level. However, I could reasonably link a patient's clinical improvement to the psychoactive effects of a particular orthomolecular intervention.

Second, the psychoactive effects of orthomolecules are far less likely to result in dangerous shifts in a patient's mental state. It is known that psychiatric medications can be associated with violence (Moore, Glenmullen, & Furberg, 2010), suicide (Björkenstam et al, 2013), and even homicide (Breggin, 2008; Lucire & Crotty, 2011). To my knowledge, there has never been any published report linking an orthomolecule to these extreme shifts in mental states. I do not mean to suggest, however, that orthomolecules are exempt from being associated with rare and worrisome psychoactive effects. There have been case reports, for instance, linking glutamine (Mebane, 1984) and SAMe (Kagan, Sultzer, Rosenlicht, & Gerner, 1990) to triggering mania even among patients with no known history of bipolar disorder. The point is that the risks of severe psychoactive effects are much greater with psychiatric medication compared to the risks associated with the therapeutic use of orthomolecules.

Third, this approach does not have to further stigmatize patients. The contemporary approach to psychiatric treatment can reinforce notions of being "brain-disordered." Patients can sometimes feel as though they have something wrong within their brains, and that psychiatric medications are required to fix these intrinsic biochemical abnormalities. Many patients also become subsumed by their mental disorder diagnoses and overidentify themselves within this disordered framework of self. It is not uncommon to hear a patient say, "I did this because of my ADD." or "I couldn't control my anger because I am borderline." Contrary to what many people believe, the provision of mental disorder diagnoses have been associated with the perpetuation of stigma (e.g., see "failure to reduce stigma" in Deacon, 2013, p. 852), and exacerbated perceptions of being abnormal and distinct from the rest of the population (Lebowitz & Ahn, 2014).

The approach advocated here, unlike the contemporary approach, does not have to reinforce notions of brain-based biochemical imbalances. Such delinking of treatment to brain-based biochemical imbalances should open clinician-patient interactions to greater empathy, kindness, affirmation, respect, and a more authentic appreciation of human suffering. In addition to an appropriate clinical examination that might involve some combination of metabolic testing and differential diagnosing (i.e., to exclude organic disease and other potential causes), a robust inventory of a patient's signs and/or symptoms can help the clinician to identify potentially useful orthomolecular interventions to lessen (or counteract) the patient's manifestations of mental distress.

Conclusion

Basing orthomolecular interventions on their psychoactive effects should be em-

braced because it is more congruent with how patients' report on their progress, more encouraging because psychoactive effects are more readily demonstrable compared to outcomes associated with unproven brain-based biochemical imbalances, and more humanistic and life-affirming because this approach is generally very safe and should reduce some of the stigma associated with having mental disorder diagnoses.

Acknowledgements

I thank Mr. Bob Sealey for his helpful editing suggestions and input on the contents of this paper.

Competing Interests

The author declares that he has no competing interests.

References

Abdou, A. M., Higashiguchi, S., Horie, K., Kim, M., Hatta, H., & Yokogoshi, H. (2006). Relaxation and immunity enhancement effects of ?-aminobutyric acid (GABA) administration in humans. *Biofactors,* 26(3), 201-208.

Abou-Saleh, M. T., & Coppen, A. (2006). Folic acid and the treatment of depression. *Journal of Psychosomatic Research,* 61(3), 285-287.

Adler, L. A., Edson, R., Lavori, P., Peselow, E., Duncan, E., Rosenthal, M., et al. (1998). Long-term treatment effects of vitamin E for tardive dyskinesia. *Biological Psychiatry,* 43(12), 868-872.

Akhondzadeh, S., Mohammadi, M., & Khademi, M. (2004). Zinc sulfate as an adjunct to methylphenidate for the treatment of attention deficit hyperactivity disorder in children: A double blind and randomized trial [ISRCTN64132371]. *BMC psychiatry,* 4(9).

Alvarez, X. A., Mouzo, R., Pichel, V., Perez, P., Laredo, M., Fernandez-Novoa, L., et al. (1999). Double-blind placebo-controlled study with citicoline in APOE genotyped Alzheimer's disease patients. Effects on cognitive performance, brain bioelectrical activity and cerebral perfusion. *Methods and Findings in Experimental and Clinical Pharmacology,* 21(9), 633-44.

Amital, D., Vishne, T., Rubinow, A., & Levine, J. (2006). Observed effects of creatine monohydrate in a patient with depression and fibromyalgia. *American Journal of Psychiatry,* 163(10), 1840-1841.

Amital, D., Vishne, T., Roitman, S., Kotler, M., & Levine, J. (2006). Open study of creatine monohydrate in treatment-resistant posttraumatic stress disorder. *Journal of Clinical Psychiatry,* 67(5), 836-837.

Amr, M., El-Mogy, A., Shams, T., Vieira, K., & Lakhan, S. E. (2013). Efficacy of vitamin C as an adjunct to fluoxetine therapy in pediatric major depressive disorder: A randomized, double-blind, placebo-controlled pilot study. *Nutrition Journal,* 12(31).

Arasteh, K. (1994). A beneficial effect of calcium intake on mood. *Journal of Orthomolecular Medicine,* 9(4), 199-204.

Banderet, L. E., & Lieberman, H. R. (1989). Treatment with tyrosine, a neurotransmitter precursor, reduces environmental stress in humans. *Brain Research Bulletin,* 22(4), 759-762.

Barak, Y., Swartz, M., Shamir, E., Stein, D., & Weizman, A. (1998). Vitamin E (?-tocopherol) in the treatment of tardive dyskinesia: A statistical meta-analysis. *Annals of Clinical Psychiatry,* 10(3), 101-105.

Barragán-Rodríguez, L., Rodríguez-Morán, M., & Guerrero-Romero, F. (2008). Efficacy and safety of oral magnesium supplementation in the treatment of depression in the elderly with type 2 diabetes: A randomized, equivalent trial. *Magnesium Research,* 21(4), 218-223.

Beckmann, H., Strauss, M.A., & Ludolph E. (1974). Dl-phenylalanine in depressed patients: An open study. *Journal of Neural Transmission,* 41(2-3), 123-134.

Beckmann, H., Athen, D., Olteanu, M., & Zimmer, R. (1970). DL-phenylalanine versus imipramine: A double-blind controlled study. *Archiv für Psychiatrie und Nervenkrankheiten,* 227(1), 49-58.

Benjamin, J., Levine, J., Fux, M., Aviv, A., Levy, D., & Belmaker, R. (1995). Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder. *American Journal of Psychiatry,* 152(7), 1084-1086.

Berk, M., Dean, O., Cotton, S. M., Gama, C. S., Kapczinski, F., Fernandes, B. S., et al. (2011). The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: An open label trial. *Journal of Affective Disorders,* 135(1), 389-394.

Berk, M., Copolov, D. L., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., et al. (2008a). N-acetyl cysteine for depressive symptoms in bipolar disorder—a double-blind randomized placebo-controlled trial. *Biological Psychiatry,* 64(6), 468-475.

Berk, M., Copolov, D., Dean, O., Lu, K., Jeavons, S., Schapkaitz, I., et al. (2008b). N-acetyl cysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. *Biological Psychiatry,* 64(5), 361-368.

Bilici, M., Yıldırım, F., Kandil, S., Bekaroʔlu, M., Yıldırmıʔ, S., Deʔer, O., et al. (2004). Double-blind, placebo-controlled study of zinc sulfate in the treatment of attention deficit hyperactivity disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry,* 28(1), 181-190.

Birdsall, T. C. (1998). 5-Hydroxytryptophan: A clin-

ically-effective serotonin precursor. *Alternative Medicine Review,* 3(4), 271-280.

Birkmayer, J. (1996). Coenzyme nicotinamide adenine dinucleotide: New therapeutic approach for improving dementia of the Alzheimer type. *Annals of Clinical & Laboratory Science,* 26(1), 1-9.

Birkmayer, J., & Birkmayer, W. (1991). The coenzyme nicotinamide adenine dinucleotide (NADH) as biological antidepressive agent: Experience with 205 patients. *New Trends Clinical Neuropharmacology,* 5(3/4), 19-25.

Birkmayer, W., Riederer, P., Linauer, W., & Knoll, J. (1984). L-deprenyl plus L-phenylalanine in the treatment of depression. *Journal of Neural Transmission,* 59(1), 81-87.

Björkenstam, C., Möller, J., Ringbäck, G., Salmi, P., Hallqvist, J., & Ljung, R. (2013). An association between initiation of selective serotonin reuptake inhibitors and suicide-a nationwide register-based case-crossover study. PloS One, 8(9), e73973.

Bloch, M. H., & Qawasmi, A. (2011). Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: Systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry,* 50(10), 991-1000.

Blum, K., Trachtenberg, M.C., Elliot, C.E., Dingler, L., & Sexton, R. L. (1989). Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and polydrug abusers: Double-blind placebo-controlled study of the nutritional adjunct SAAVETM. *Alcohol,* 5(6), 481-493.

Blum, K., Allison, D., Trachtenberg, M. C., Williams, R.W., & Loeblich, L. A. (1988). Reduction of both drug hunger and withdrawal against advice rate of cocaine abusers in a 30-day inpatient treatment program by the neuronutrient TropamineTM. *Current Therapeutic Research,* 43(6), 1204-1214.

Blum, K., & Trachtenberg, M.C. (1988). Neurogenetic deficits caused by alcoholism: Restoration by SAAVETM, a neuronutrient intervention adjunct. *Journal of Psychoactive Drugs,* 20(3), 297-313.

Bowen, D. J., Spring, B., & Fox, E. (1991). Tryptophan and high-carbohydrate diets as adjuncts to smoking cessation therapy. *Journal of Behavioral Medicine,* 14(2), 97-110.

Braverman, E. R., Pfeiffer, C. C., Blum, K., & Smayda, R. (1997). Glutamate amino acids. *In The healing nutrients within* (2nd ed., pp. 238-279). 2nd ed. New Canaan, CT: Keats Publishing.

Breggin, P. R. (2008). *Medication madness. The role of psychiatric drugs in cases of violence, suicide, and crime.* New York, NY: St. Martin's Griffin.

Brenner, A. (1982). The effects of megadoses of selected B complex vitamins on children with hyperkinesis: Controlled studies with long-term follow-up. *Journal of Learning Disabilities,* 15(5), 258-264.

Brody, S., Preut, R., Schommer, K., & Schürmeyer, T. H. (2002). A randomized controlled trial of high dose ascorbic acid for reduction of blood pressure, cortisol, and subjective responses to psychological stress. *Psychopharmacology,* 159(3), 319-324.

Brown, E. S., Gorman, A. R., & Hynan, L. S. (2007). A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. *Journal of Clinical Psychopharmacology,* 27(5), 498-502.

Bruner, A. B., Joffe, A., Duggan, A. K., Casella, J. F., & Brandt, J. (1996). Randomised study of cognitive effects of iron supplementation in non-anaemic iron-deficient adolescent girls. *The Lancet,* 348(9033), 992-996.

Brzezinski, A., Vangel, M. G., Wurtman, R. J., Norrie, G., Zhdanova, I., Ben-Shushan, A., et al. (2005). Effects of exogenous melatonin on sleep: A meta-analysis. S*leep Medicine Reviews,* 9(1), 41-50.

Bulut, M., Savas, H. A., Altindag, A., Virit, O., & Dalkilic, A. (2009). Beneficial effects of N-acetylcysteine in treatment resistant schizophrenia. *World Journal of Biological Psychiatry,* 10(4-2), 626-628.

Bunney Jr, W. E., & Potkin, S. G. (1988). S—adenosylmethionine treatment of depression: A controlled clinical trial. *American Journal of Psychiatry,* 145(11), 10-1114.

Buydens-Branchey, L., Branchey, M., & Hibbeln, J. R. (2008). Associations between increases in plasma n-3 polyunsaturated fatty acids following supplementation and decreases in anger and anxiety in substance abusers. *Progress in Neuro-Psychopharmacology and Biological Psychiatry,* 32(2), 568-575.

Carlomagno, G., Unfer, V., Buffo, S., & D'Ambrosio, F. (2011). Myo?inositol in the treatment of premenstrual dysphoric disorder. *Human Psychopharmacology: Clinical and Experimental,* 26(7), 526-530.

Casey, D. E., & Denney, D. (1975). Deanol in the treatment of tardive dyskinesia. *American Journal of Psychiatry,* 132(8), 864-867.

Chengappa, K. R., Levine, J., Gershon, S., Mallinger, A. G., Hardan, A., Vagnucci, A., et al. (2000). Inositol as an add-on treatment for bipolar depression. *Bipolar Disorders,* 2(1), 47-55.

Chouinard, G., Young, S., Annable, L., & Sourkes, T. (1979). Tryptophan-nicotinamide, imipramine and their combination in depression. *Acta Psychiatrica Scandinavica,* 59(4), 395-414.

Chouinard, G., Young, S. N., Annable, L., & Sourkes, T. L. (1977). Tryptophan-nicotinamide combination in depression. *Lancet,* 1(8005), 249.

Clayton, E., Hanstock, T., Hirneth, S., Kable, C., Garg, M., & Hazell, P. (2009). Reduced mania and depression in juvenile bipolar disorder associated with long-chain ?-3 polyunsaturated fatty acid supplementation. *European Journal of Clinical Nutrition,* 63(8), 1037-1040.

Cleveland, W. L., DeLaPaz, R. L., Fawwaz, R. A., & Challop, R. S. (2010). High-dose glycine treat-

ment of refractory obsessive-compulsive disorder and body dysmorphic disorder in a 5-year period. *Neural Plasticity,* 2009 (Article ID 768398).

Coleman, N., Dexheimer, P., DiMascio, A., Redman, W., & Finnerty, R. (1976). Deanol in the treatment of hyperkinetic children. *Psychosomatics,* 17(2), 68-72.

Coppen, A., & Bailey, J. (2000). Enhancement of the antidepressant action of fluoxetine by folic acid: A randomised, placebo controlled trial. *Journal of Affective Disorders,* 60(2), 121-130.

Cotroneo, A. M., Castagna, A., Putignano, S., Lacava, R., Fantò, F., Monteleone, F., et al. (2013). Effectiveness and safety of citicoline in mild vascular cognitive impairment: The IDEALE study. *Clinical Interventions in Aging,* 8, 131-137.

Cox, I., Campbell, M., & Dowson, D. (1991). Red blood cell magnesium and chronic fatigue syndrome. *The Lancet,* 337(8744), 757-760.

Daniela, J., Aikaterini, M., Miro, S., Yasushi, M., & Roman, D. (2005). Subchronic treatment with amino acid mixture of L-lysine and L-arginine modifies neuroendocrine activation during psychosocial stress in subjects with high trait anxiety. *Nutritional Neuroscience,* 8(3), 155-160.

Dakhale, G., Khanzode, S., Khanzode, S., & Saoji, A. (2005). Supplementation of vitamin C with atypical antipsychotics reduces oxidative stress and improves the outcome of schizophrenia. *Psychopharmacology,* 182(4), 494-498.

Davidson, J. R., Abraham, K., Connor, K. M., & McLeod, M. N. (2003). Effectiveness of chromium in atypical depression: A placebo-controlled trial. *Biological Psychiatry,* 53(3), 261-264.

de Oliveira, I. J. L., de Souza, V. V., Motta, V., & Da-Silva, S. L. (2015). Effects of oral vitamin C supplementation on anxiety in students: A double-blind, randomized, placebo-controlled trial. *Pakistan Journal of Biological Sciences,* 18(1), 11-18.

Deacon, B. J. (2013). The biomedical model of mental disorder: A critical appraisal of its validity, utility, and effects of psychotherapy research. *Clinical Psychology Review,* 33(7), 846-861.

Deijen, J., & Orlebeke, J. (1994). Effect of tyrosine on cognitive function and blood pressure under stress. *Brain Research Bulletin,* 33(3), 319-323.

Deijen, J., Wientjes, C., Vullinghs, H., Cloin, P., & Langefeld, J. (1999). Tyrosine improves cognitive performance and reduces blood pressure in cadets after one week of a combat training course. *Brain Research Bulletin,* 48(2), 203-209.

Delwaide, P., Gyselynck-Mambourg, A., Hurlet, A., & Ylieff, M. (1986). Double-blind randomized controlled study of phosphatidylserine in senile demented patients. *Acta Neurologica Scandinavica,* 73(2), 136-140.

Demarin, V., Podobnik, S., Storga-Tomic, D., & Kay, G. (2003). Treatment of Alzheimer's disease with stabilized oral nicotinamide adenine dinucleotide: A randomized, double-blind study. *Drugs Under Experimental and Clinical Research,* 30(1), 27-33.

De Silva, L., & Huang, C. (1975). Deanol in tardive dyskinesia. *British Medical Journal,* 3(5981), 466-466.

De Souza, M. C., Walker, A. F., Robinson, P. A., & Bolland, K. (2000). A synergistic effect of a daily supplement for 1 month of 200 mg magnesium plus 50 mg vitamin B6 for the relief of anxiety-related premenstrual symptoms: A randomized, double-blind, crossover study. *Journal of Women's Health & Gender-Based Medicine,* 9(2), 131-139.

Docherty, J. P., Sack, D. A., Roffman, M., Finch, M., & Komorowski, J. R. (2005). A double-blind, placebo-controlled, exploratory trial of chromium picolinate in atypical depression: Effect on carbohydrate craving. *Journal of Psychiatric Practice,* 11(5), 302-314.

Dolina, S., Margalit, D., Malitsky, S., & Rabinkov, A. (2014). Attention-deficit hyperactivity disorder (ADHD) as a pyridoxine-dependent condition: Urinary diagnostic biomarkers. *Medical Hypotheses,* 82(1), 111-116.

Dollins, A. B., Krock, L. P., Storm, W. F., Wurtman, R. J., & Lieberman, H. R. (1995). L-tyrosine ameliorates some effects of lower body negative pressure stress. *Physiology & Behavior,* 57(2), 223-230.

Eby, G. A., & Eby, K. L. (2006). Rapid recovery from major depression using magnesium treatment. *Medical Hypotheses,* 67(2), 362-370.

Elizur, A., Kofman, O., & Belmaker, R. (1995). Double-blind, controlled trial of inositol treatment of depression. *American Journal of Psychiatry,* 152(5), 792-794.

Ellis, F., & Nasser, S. (1973). A pilot study of vitamin B 12 in the treatment of tiredness. *British Journal of Nutrition,* 30(2), 277-283.

Fann, W. E., Sullivan III, J. L., Miller, R. D., & McKenzie, G. M. (1975). Deanol in tardive dyskinesia: A preliminary report. *Psychopharmacologia,* 42(2), 135-137.

Facchinetti, F., Borella, P., Sances, G., Fioroni, L., Nappi, R. E., & Genazzani, A. R. (1991). Oral magnesium successfully relieves premenstrual mood changes. *Obstetrics & Gynecology,* 78(2), 177-181.

Ferracioli-Oda, E., Qawasmi, A., & Bloch, M. H. (2013). Meta-analysis: Melatonin for the treatment of primary sleep disorders. *PloS One,* 8(5), e63773.

Forester, B. P., Zuo, C. S., Ravichandran, C., Harper, D. G., Du, F., Kim, S., et al. (2012). Coenzyme Q10 effects on creatine kinase activity and mood in geriatric bipolar depression. *Journal of Geriatric Psychiatry and Neurology,* 25(1), 43-50.

Fovall, P., Dysken, M., Lazarus, L., Davis, J., Kahn, R., Jope, R., et al. (1980). Choline bitartrate treatment of Alzheimer-type dementias. *Communications in Psychopharmacology,* 4(2), 141-145.

Fux, M., Levine, J., Aviv, A., & Belmaker, R. (1996).

Inositol treatment of obsessive-compulsive disorder. *American Journal of Psychiatry,* 153(9), 1219-1221.

García-Cobos, R., Frank-García, A., Gutiérrez-Fernández, M., & Díez-Tejedor, E. (2010). Citicoline, use in cognitive decline: Vascular and degenerative. *Journal of the Neurological Sciences,* 299(1), 188-192.

Garzya, G., Corallo, D., Fiore, A., Lecciso, G., Petrelli, G., & Zotti, C. (1989). Evaluation of the effects of L-acetylcarnitine on senile patients suffering from depression. *Drugs Under Experimental and Clinical Research,* 16(2), 101-106.

Gelber, D., Levine, J., & Belmaker, R. (2001). Effect of inositol on bulimia nervosa and binge eating. *International Journal of Eating Disorders,* 29(3), 345-348.

Gelenberg, A. J., Wojcik, J. D., Gibson, C. J., & Wurtman, R. J. (1983). Tyrosine for depression. *Journal of Psychiatric Research,* 17(2), 175-180.

Gelenberg, A. J., Wojcik, J. D., Growdon, J., Sved, A., & Wurtman, R. (1980).Tyrosine for the treatment of depression. *American Journal of Psychiatry,* 137(5), 622-623.

Ghadirian, A., Murphy, B., & Gendron, M. (1998). Efficacy of light versus tryptophan therapy in seasonal affective disorder. *Journal of Affective disorders,* 50(1), 23-27.

Grant, J. E., Odlaug, B. L., & Kim, S. W. (2009). N-acetylcysteine, a glutamate modulator, in the treatment of trichotillomania: A double-blind, placebo-controlled study. *Archives of General Psychiatry,* 66(7), 756-763.

Gray, K. M., Carpenter, M. J., Baker, N. L., DeSantis, S. M., Kryway, E., Hartwell, K. J., et al. (2012). A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. *American Journal of Psychiatry,* 169(8), 805-812.

Gray, K. M., Watson, N. L., Carpenter, M. J., & LaRowe, S. D. (2010). N-acetylcysteine (NAC) in young marijuana users: An open-label pilot study. *American Journal on Addictions,* 19(2), 187-189..

Gregory, I. (1952). Nicotinic acid therapy in psychoses of senility. *American Journal of Psychiatry,* 108(12), 888-895.

Greenberg, W. M., Benedict, M. M., Doerfer, J., Perrin, M., Panek, L., Cleveland, W. L., et al. (2009). Adjunctive glycine in the treatment of obsessive-compulsive disorder in adults. *Journal of Psychiatric Research,* 43(6), 664-670.

Guaraldi, G. P., Fava, M., Mazzi, F., & la Greca, P. (1993). An open trial of methyltetrahydrofolate in elderly depressed patients. *Annals of Clinical Psychiatry,* 5(2), 101-105.

Harrison-Hohner, J., Coste, S., Dorato, V., Curet, L., McCarron, D., & Hatton, D. (2001). Prenatal calcium supplementation and postpartum depression: An ancillary study to a randomized trial of calcium for prevention of preeclampsia. *Archives of Women's Mental Health,* 3(4), 141-146.

Hirayama, S., Terasawa, K., Rabeler, R., Hirayama, T., Inoue, T., Tatsumi, Y., et al. (2014). The effect of phosphatidylserine administration on memory and symptoms of attention-deficit hyperactivity disorder: A randomised, double-blind, placebo-controlled clinical trial. *Journal of Human Nutrition and Dietetics,* 27(suppl. 2), 284-291.

Heresco-Levy, U., Ermilov, M., Lichtenberg, P., Bar, G., & Javitt, D. C. (2004). High-dose glycine added to olanzapine and risperidone for the treatment of schizophrenia. *Biological Psychiatry,* 55(2), 165-171.

Heresco-Levy, U., Javitt, D. C., Ermilov, M., Mordel, C., Silipo, G., & Lichtenstein, M. (1999). Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Archives of *General Psychiatry,* 56(1), 29-36.

Heresco-Levy, U., Javitt, D. C., Ermilov, M., Mordel, C., Horowitz, A., & Kelly, D. (1996). Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia. *British Journal of Psychiatry,* 169(5), 610-617.

Hoffer, A. (1994). Chronic schizophrenia patients treated ten years or more. *Journal of Orthomolecular Medicine*, 9(1), 7-37.

Hoffer, A. (1974). Senility and chronic malnutrition. *Orthomolecular Psychiatry,* 3(1), 2-19.

Hoffer, A. (1971). Vitamin B3 dependent child. *Schizophrenia,* 3(2), 107-113.

Hoffer, A. (1962). Nicotinic acid in confusional and drug-induced psychosis. *Niacin therapy in psychiatry* (pp. 72-107). Springfield, MA: Charles C Thomas.

Hoffer, A., Callbeck, M. J. (1962). *Nicotinic acid and nicotinamide in treatment of schizophrenia. Niacin therapy in psychiatry* (pp. 35-71). Springfield, MA: Charles C Thomas.

Hoffer, A., Osmond, H., Callbeck, M., & Kahan, I. (1957). Treatment of schizophrenia with nicotinic acid and nicotinamide. *Journal of Clinical & Experimental Psychopathology,* 18(2), 131-158.

Jangid, P., Malik, P., Singh, P., & Sharma, M. (2013). Comparative study of efficacy of L-5-hydroxytryptophan and fluoxetine in patients presenting with first depressive episode. *Asian Journal of Psychiatry,* 6(1), 29-34.

Javitt, D. C., Zylberman, I., Zukin, S. R., Heresco-Levy, U., & Lindenmayer, J-P. (1994). Amelioration of negative symptoms in schizophrenia by glycine. *The American Journal of Psychiatry,* 151(8), 1234-1236.

Jorde, R., Sneve, M., Figenschau, Y., Svartberg, J., & Waterloo, K. (2008). Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: Randomized double blind trial. *Journal of Internal Medicine,* 264(6), 599-609.

Juneja, L. R., Chu, D., Okubo, T., Nagato, Y., & Yokogoshi, H. (1999). L-theanine—a unique amino

acid of green tea and its relaxation effect in humans. *Trends in Food Science & Technology,* 10(6), 199-204.

Junker, D., Steigleider, P., & Gattaz, W. (1992). Alpha-tocopherol in the treatment of tardive dyskinesia. *Schizophrenia Research,* 6(2), 122-123.

Kagan, B. L., Sultzer, D. L., Rosenlicht, N., & Gerner, R. H. (1990). Oral S-adenosylmethionine in depression: A randomized, double-blind, placebo-controlled trial. *American Journal of Psychiatry,* 147(5), 591-595.

Kahn, R., & Westenberg, H. G. (1985). L-5-Hydroxytryptophan in the treatment of anxiety disorders. *Journal of Affective Disorders,* 8(2), 197-200.

Kashanian, M., Mazinani, R., & Jalalmanesh, S. (2007). Pyridoxine (vitamin B6) therapy for premenstrual syndrome. *International Journal of Gynecology & Obstetrics,* 96(1), 43-44.

Kennedy, D. O., Veasey, R., Watson, A., Dodd, F., Jones, E., Maggini, S., & Haskell, C. F. (2010). Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males. *Psychopharmacology* (Berlin), 211(1), 55-68.

Khoraminya, N., Tehrani-Doost, M., Jazayeri, S., Hosseini, A., & Djazayery, A. (2013). Therapeutic effects of vitamin D as adjunctive therapy to fluoxetine in patients with major depressive disorder. A*ustralian and New Zealand Journal of Psychiatry,* 47(3), 271-275.

Kiecolt-Glaser, J. K., Belury, M. A., Andridge, R., Malarkey, W. B., & Glaser, R. (2011). Omega-3 supplementation lowers inflammation and anxiety in medical students: A randomized controlled trial. *Brain, Behavior, and Immunity,* 25(8), 1725-1734.

Konofal, E., Cortese, S., Lecendreux, M., Arnulf, I., & Mouren, M. C. (2005). Effectiveness of iron supplementation in a young child with attention-deficit/hyperactivity disorder. *Pediatrics,* 116(5), e732-e734.

Konofal, E., Lecendreux, M., Deron, J., Marchand, M., Cortese, S., Zaïm, M., et al. (2008). Effects of iron supplementation on attention deficit hyperactivity disorder in children. *Pediatric Neurology,* 38(1), 20-26.

Kontush, K., & Schekatolina, S. (2004). Vitamin E in neurodegenerative disorders: Alzheimer's disease. *Annals of the New York Academy of Sciences,* 1031(1), 249-262.

Krikorian, R., Eliassen, J. C., Boespflug, E. L., Nash, T. A., & Shidler, M. D. (2010). Improved cognitive-cerebral function in older adults with chromium supplementation. *Nutritional Neuroscience,* 13(3), 116-122.

Kunin, R. A. (1976). Manganese and niacin in the treatment of drug-induced dyskinesias. *Journal of Orthomolecular Psychiatry,* 5(1), 4-27.

Lafleur, D. L., Pittenger, C., Kelmendi, B., Gardner, T., Wasylink, S., Malison, R. T., et al. (2006). N-acetylcysteine augmentation in serotonin reuptake inhibitor refractory obsessive-compulsive disorder. *Psychopharmacology* (Berl), 184(2), 254-256.

Lai, J., Moxey, A., Nowak, G., Vashum, K., Bailey, K., & McEvoy, M. (2012). The efficacy of zinc supplementation in depression: Systematic review of randomised controlled trials. *Journal of Affective Disorders,* 136(1-2), e31-e39.

LaRowe, S. D., Mardikian, P., Malcolm, R., Myrick, H., Kalivas, P., McFarland, K., et al. (2006). Safety and tolerability of N-acetylcysteine in cocaine-dependent individuals. *American Journal on Addictions,* 15(1), 105-110.

Lebowitz, M. S., & Ahn, W. (2014). Effects of biological explanations for mental disorders on clinicians' empathy. *Proceedings of the National Academy of Sciences,* 111(50), 17786-17790.

Lerner, V., Kaptsan, A., Miodownik, C., & Kotler, M. (1999). Vitamin B6 in treatment of tardive dyskinesia: A preliminary case series study. *Clinical Neuropharmacology,* 22(4), 241-243.

Lerner, V., & Liberman, M. (1998). Movement disorders and psychotic symptoms treated with pyridoxine: A case report. *Journal of Clinical Psychiatry,*59(11), 623-624.

Levine, J., Stahl, Z., Sela, B., Ruderman, V., Shumaico, O., Babushkin, I., et al. (2006). Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. *Biological Psychiatry,* 60(3), 265-269.

Lewis, J. E., Tiozzo, E., Melillo, A. B., Leonard, S., Chen, L., Mendez, A., et al. (2013). The effect of methylated vitamin B complex on depressive and anxiety symptoms and quality of life in adults with depression. *ISRN Psychiatry,* 1-7. doi:10.1155/2013/621453

Lewis, J., & Young, R. (1975). Deanol and methylphenidate in minimal brain dysfunction. *Clinical Pharmacology and Therapeutics,* 17(5), 534-540.

Lohr, J. B., Cadet, J. L., Lohr, M. A., Larson, L., Wasll, E., Wade, L., et al (1988). Vitamin E in the treatment of tardive dyskinesia: The possible involvement of free radical mechanisms. *Schizophrenia Bulletin,* 14(2), 291-296.

Loriaux, S., Deijen, J., Orlebeke, J., & De Swart, J. (1985). The effects of nicotinic acid and xanthinol nicotinate on human memory in different categories of age. *Psychopharmacology,* 87(4), 390-395.

Lu, K., Gray, M. A., Oliver, C., Liley, D. T., Harrison, B. J., Bartholomeusz, C. F., et al. (2004). The acute effects of L?theanine in comparison with alprazolam on anticipatory anxiety in humans. *Human Psychopharmacology: Clinical and Experimental,* 19(7), 457-465.

Lucire, Y., & Crotty, C. (2011). Antidepressant-induced akathisia-related homicides associated with diminishing mutations in metabolizing genes of the CYP450 family.*Pharmacogenomics and personalized medicine*, 4(1), 65-81.

Lyon, M. R., Kapoor, M. P., & Juneja, L. R. (2011).

The effects of L-theanine (Suntheanine) on objective sleep quality in boys with attention deficit hyperactivity disorder (ADHD): A randomized, double-blind, placebo-controlled clinical trial. *Alternative Medicine Review,* 16(4), 348-354.

Lyoo, I. K., Yoon, S., Kim, T., Hwang, J., Kim, J. E., Won, W., et al. (2012). A randomized, double-blind placebo-controlled trial of oral creatine monohydrate augmentation for enhanced response to a selective serotonin reuptake inhibitor in women with major depressive disorder. *American Journal of Psychiatry,* 169(9), 937-945.

MacSweeney, D. A. (1975). Treatment of unipolar depression. *Lancet,* 2(7933), 510-511.

Magalhães, P. V., Dean, O. M., Bush, A. I., Copolov, D. L., Malhi, G. S., Kohlmann, K., et al. (2011). N-acetylcysteine for major depressive episodes in bipolar disorder. *Revista Brasileira de Psiquiatria,* 33(4), 374-378.

Mahoney, C. R., Castellani, J., Kramer, F. M., Young, A., & Lieberman, H. R. (2007). Tyrosine supplementation mitigates working memory decrements during cold exposure. *Physiology & Behavior,* 92(4), 575-582.

Malaguarnera, M., Gargante, M. P., Cristaldi, E., Colonna, V., Messano, M., Koverech, A., et al. (2008). Acetyl L-carnitine (ALC) treatment in elderly patients with fatigue. *Archives of Gerontology and Geriatrics,* 46(2), 181-190.

Maggioni, M., Picotti, G., Bondiolotti, G., Panerai, A., Cenacchi, T., Nobile, P., et al. (1990). Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. *Acta Psychiatrica Scandinavica,* 81(3), 265-270.

Manor, I., Magen, A., Keidar, D., Rosen, S., Tasker, H., Cohen, T., et al. (2012). The effect of phosphatidylserine containing Omega3 fatty-acids on attention-deficit hyperactivity disorder symptoms in children: A double-blind placebo-controlled trial, followed by an open-label extension. *European Psychiatry,* 27(5), 335-342.

Mardikian, P. N., LaRowe, S. D., Hedden, S., Kalivas, P. W., & Malcolm, R. J. (2007). An open-label trial of N-acetylcysteine for the treatment of cocaine dependence: A pilot study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry,* 31(2), 389-394.

Mazloom, Z., Ekramzadeh, M., & Hejazi, N. (2013). Efficacy of supplementary vitamins C and E on anxiety, depression and stress in type 2 diabetic patients: A randomized, single-blind, placebo-controlled trial. *Pakistan Journal of Biological Sciences,* 16(22), 1597-1600.

McClung, J. P., Karl, J. P., Cable, S. J., Williams, K. W., Nindl, B. C., Young, A. J., et al. (2009). Randomized, double-blind, placebo-controlled trial of iron supplementation in female soldiers during military training: Effects on iron status, physical performance, and mood. *American Journal of Clinical Nutrition,* 90(1), 124-131.

McGrath, R. E., Buckwald, B., & Resnick, E. V. (1990). The effect of L-tryptophan on seasonal affective disorder. *Journal of Clinical Psychiatry,* 51(4), 162-163.

McLeod, M. N., & Golden, R. N. (1999). Chromium potentiation of antidepressant pharmacotherapy for dysthymic disorder in 5 patients. *Journal of Clinical Psychiatry,* 60(4), 237-240.

McLeod, M. N., & Golden, R. N. (2000).Chromium treatment of depression. *The International Journal of Neuropsychopharmacology,* 3(04), 311-314.

Miller, A. L. (2008). The methylation, neurotransmitter, and antioxidant connections between folate and depression. *Alternative Medicine Review,* 13(3), 216-227.

Mebane, A. (1984). L-Glutamine and mania. *American Journal of Psychiatry,* 141(10), 1302-1303.

Meyers, S. (2000). Use of neurotransmitter precursors for treatment of depression. *Alternative Medicine Review,* 5(1), 64-71.

Miller, E. (1974). Deanol in the treatment of levodopa?induced dyskinesias. *Neurology,* 24(2), 116-116.

Miodownik, C., Lerner, V., Statsenko, N., Dwolatzky, T., Nemets, B., Berzak, E., et al. (2006). Vitamin B6 versus mianserin and placebo in acute neuroleptic-induced akathisia: A randomized, double-blind, controlled study. *Clinical Neuropharmacology,* 29(2), 68-72.

Mitchell, J. A. (2007). The effect of folic acid and B12 on depression: Twelve cases. *Journal of Orthomolecular Medicine,* 22(4), 183-192.

Mocking, R., Harmsen, I., Assies, J., Koeter, M., Ruhé, H., & Schene, A. (2016). Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Translational Psychiatry,* 6(3), e756.

Moncrieff, J., & Cohen, D. (2006). Do antidepressants cure or create abnormal brain states? *PLoS Medicine,* 3(7), e240.

Moncrieff, J., & Cohen, D. (2009). How do psychiatric drugs work? *British Medical Journal,* 338(b1963), 1535-1537.

Moncrieff, J. (2009). A critique of the dopamine hypothesis of schizophrenia and psychosis. *Harvard Review of Psychiatry,* 17(3), 214-225.

Moncrieff, J. (2011). Questioning the 'neuroprotective' hypothesis: Does drug treatment prevent brain damage in early psychosis or schizophrenia? *British Journal of Psychiatry,* 198(2), 85-87.

Moncrieff, J. (2013). Magic bullets for mental disorders: The emergence of the concept of an "antipsychotic" drug. Journal of the History of Neuroscience: *Basic and Clinical Perspectives,* 22(1), 30-46.

Montgomery, S. A., Thal, L., & Amrein, R. (2003). Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. *International Clinical Psychopharmacology,* 18(2), 61-71.

Moore, T. J., Glenmullen, J., & Furberg, C. D. (2010). Prescription drugs associated with reports of violence towards others. PLoS One, 5(12), e15337.

Mousain-Bosc, M., Roche, M., Polge, A., Pradal-Prat, D., Rapin, J., & Bali, J. (2006). Improvement of neurobehavioral disorders in children supplemented with magnesium-vitamin B6. *Magnesium Research,* 19(1), 53-62.

Mouret, J., Sanchez, P., Taillard, J., Lemoine, P., Robelin, N., & Canini, F. (1988). Treatment of narcolepsy with L-tyrosine. *The Lancet,* 332(8626), 1458-1459.

Mukai, T., Kishi, T., Matsuda, Y., & Iwata, N. (2014). A meta-analysis of inositol for depression and anxiety disorders. *Human Psychopharmacology: Clinical and Experimental,* 29(1), 55-63.

Neri, D. F., Wiegmann, D., Stanny, R. R., Shappell, S. A., McCardie, A., & McKay, D. L. (1995). The effects of tyrosine on cognitive performance during extended wakefulness. *Aviation, Space, and Environmental Medicine,* 66(4), 313-319.

Newbold, H. (1989). Vitamin B-12b as an antidote for over-sedation. Medical Hypotheses, 30(1), 1-3.

Nierenberg, A. A., Ostacher, M. J., Calabrese, J. R., Ketter, T. A., Marangell, L. B., Miklowitz, D. J., et al. (2006). Treatment-resistant bipolar depression: A STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *American Journal of Psychiatry,* 163(2), 210-216.

Nobre, A. C., Rao, A., & Owen, G. N. (2008). L-theanine, a natural constituent in tea, and its effect on mental state. *Asian Pacific Journal of Clinical Nutrition,* 17(suppl 1), 167-168.

Nowak, G., Siwek, M., Dudek, D., Zięba, A., & Pilc, A. (2003). Effect of zinc supplementation on antidepressant therapy in unipolar depression: A preliminary placebo-controlled study. *Polish Journal of Pharmacology,* 55(6), 1143-1148.

Osmond, H., & Hoffer, A. (1962). Massive niacin treatment in schizophrenia: Review of a nine-year study. *The Lancet,* 279(7224), 316-320.

Palatnik, A., Frolov, K., Fux, M., & Benjamin, J. (2001). Double-blind, controlled, crossover trial of inositol versus fluvoxamine for the treatment of panic disorder. *Journal of Clinical Psychopharmacology,* 21(3), 335-339.

Park, S., Jung, I., Lee, W. K., Lee, Y. S., Park, H. K., Go, H. J., et al. (2011). A combination of green tea extract and l-theanine improves memory and attention in subjects with mild cognitive impairment: A double-blind placebo-controlled study. *Journal of Medicinal Food,* 14(4), 334-343.

Pettegrew, J. W., Levine, J., Gershon, S., Stanley, J. A., Servan-Schreiber, D., Panchalingam, K., et al. (2002). 31PMRS study of acetyl-L-carnitine treatment in geriatric depression: *Preliminary results. Bipolar Disorders,* 4(1), 61-66.

Prousky, J. E. (2005). Supplemental niacinamide mitigates anxiety symptoms: Three case reports. Journal of Orthomolecular Medicine, 20(3), 167-178.

Prousky, J. E. (2004). Niacinamide's potent role in alleviating anxiety with its benzodiazepine-like properties: A case report. *Journal of Orthomolecular Medicine,* 19(2), 104-110.

Rae, C., Digney, A. L., McEwan, S. R., Bates, T. C. (2003). Oral creatine monohydrate supplementation improves brain performance: A double–blind, placebo–controlled, cross–over trial. Proceedings of the Royal Society of London B: *Biological Sciences,* 270(1529), 2147-2150.

Ranjbar, E., Kasaei, M. S., Mohammad-Shirazi, M., Nasrollahzadeh, J., Rashidkhani, B., Shams, J., et al. (2013). Effects of zinc supplementation in patients with major depression: A randomized clinical trial. *Iranian Journal of Psychiatry*,8(2), 73-79.

Reimherr, F. W., Wender, P., Wood, D., & Ward, M. (1987). An open trial of L-tyrosine in the treatment of attention deficit disorder, residual type. *American Journal of Psychiatry,* 144(8), 1071-1073.

Ritsner, M. S., Miodownik, C., Ratner, Y., Shleifer, T., Mar, M., Pintov, L., & Lerner, V. (2010). L-theanine relieves positive, activation, and anxiety symptoms in patients with schizophrenia and schizoaffective disorder: An 8-week, randomized, double-blind, placebo-controlled, 2-center study. *Journal of Clinical Psychiatry,* 72(1), 1,478-42.

Rodrigues-Barata, A. R., Tosti, A., Rodríguez-Pichardo, A., & Camacho-Martínez, F. (2012). N-acetylcysteine in the treatment of trichotillomania. *International Journal of Trichology,* 4(3), 176-178.

Rogers, L., & Pelton, R. (1957). Glutamine in the treatment of alcoholism; a preliminary report. *Quarterly Journal of Studies on Alcohol,* 18(4), 581-587.

Roitman, S., Green, T., Osher, Y., Karni, N., & Levine, J. (2007). Creatine monohydrate in resistant depression: A preliminary study. *Bipolar Disorders,* 9(7), 754-758.

Sarris, J., Mischoulon, D., & Schweitzer, I. (2012). Omega-3 for bipolar disorder: Meta-analyses of use in mania and bipolar depression. *Journal of Clinical Psychiatry,* 73(1), 8-86.

Sarris, J., Murphy, J., Mischoulon, D., Papakostas, G. I., Fava, M., Berk, M., et al. (2016). Adjunctive Nutraceuticals for Depression: A Systematic Review and Meta-Analyses. *American Journal of Psychiatry,* 173 (6), 575-587.

Schneider-Helmert, D., & Spinweber, C. L. (1986). Evaluation of L-tryptophan for treatment of insomnia: A review. *Psychopharmacology,* 89(1), 1-7.

Sever, Y., Ashkenazi, A., Tyano, S., & Weizman, A. (1997). Iron treatment in children with attention deficit hyperactivity disorder. *Neuropsychobiology,* 35(4), 178-180.

Shaffer, J. A., Edmondson, D., Wasson, L. T., Falzon, L., Homma, K., Ezeokoli, N., et al. (2014). Vitamin D supplementation for depressive symptoms: A systematic review and meta-analysis

of randomized controlled trials. *Psychosomatic Medicine,*76(3), 190-196.

Shakeri, J., Khanegi, M., Golshani, S., Farnia, V., Tatari, F., Alikhani, M., et al. (2016). Effects of omega-3 supplement in the treatment of patients with bipolar I disorder. *International Journal of Preventive Medicine,* 7(1), 77.

Shipowick, C. D., Moore, C. B., Corbett, C., & Bindler, R. (2009). Vitamin D and depressive symptoms in women during the winter: A pilot study. *Applied Nursing Research,* 22(3), 221-225.

Shurtleff, D., Thomas, J. R., Schrot, J., Kowalski, K., & Harford, R. (1994). Tyrosine reverses a cold-induced working memory deficit in humans. *Pharmacology Biochemistry and Behavior,* 47(4), 935-941.

Siwek, M., Dudek, D., Paul, I. A., Sowa-Ku?ma, M., Zi?ba, A., Popik, P., et al. (2009). Zinc supplementation augments efficacy of imipramine in treatment resistant patients: A double blind, placebo-controlled study. Journal of Affective Disorders,118(1), 187-195.

Simpson, G. M., Voitashevsky, A., Young, M. A., & Lee, J. H. (1977). Deanol in the treatment of tardive dyskinesia. Psychopharmacology, 52(3), 257-261.

Smriga, M., Ando, T., Akutsu, M., Furukawa, Y., Miwa, K., & Morinaga, Y. (2007). Oral treatment with L-lysine and L-arginine reduces anxiety and basal cortisol levels in healthy humans. Biomedical Research, 28(2), 85-90.

Spagnoli, A., Lucca, U., Menasce, G., Bandera, L., Cizza, G., Forloni, G., et al. (1991). Long-term acetyl-L-carnitine treatment in Alzheimer's disease. Neurology, 41(11), 1726-1726.

Starobrat-Hermelin, B., & Kozielec, T. (1997). The effects of magnesium physiological supplementation on hyperactivity in children with attention deficit hyperactivity disorder (ADHD). Positive response to magnesium oral loading test. Magnesium Research, 10(2), 149-156.

Stoll, A. L., Sachs, G. S., Cohen, B. M., Lafer, B., Christensen, J. D., & Renshaw, P. F. (1996). Choline in the treatment of rapid-cycling bipolar disorder: Clinical and neurochemical findings in lithium-treated patients. Biological Psychiatry, 40(5), 382-388.

Stough, C., Scholey, A., Lloyd, J., Spong, J., Myers, S., & Downey, L. A. (2011). The effect of 90 day administration of a high dose vitamin B-complex on work stress. Human Psychopharmacology Clinical and Experimental, 26(7), 470-476.

Sydenstricker, V., & Cleckley, H. (1941). The effect of nicotinic acid in stupor, lethargy and various other psychiatric disorders. American Journal of Psychiatry, 98(1), 83-92.

Tempesta, E., Casella, L., Pirrongelli, C., Janiri, L., Calvani, M., & Ancona, L. (1986). L-acetylcarnitine in depressed elderly subjects. A cross-over study vs placebo. Drugs Under Experimental and Clinical Research, 13(7), 417-423.

Thompson, L., & Proctor, R. (1953). Depressive and anxiety reactions treated with nicotinic acid and phenobarbital. North Carolina Medical Journal, 14(9), 420-426.

Thomson, J., Rankin, H., Ashcroft, G., Yates, C. M., McQueen, J. K., & Cummings, S. (1982). The treatment of depression in general practice: A comparison of L-tryptophan, amitriptyline, and a combination of L-tryptophan and amitriptyline with placebo. Psychological Medicine, 12(04), 741-751.

Thys-Jacobs, S. (2000). Micronutrients and the premenstrual syndrome: The case for calcium. Journal of the American College of Nutrition, 19(2), 220-227.

Unno, K., Tanida, N., Ishii, N., Yamamoto, H., Iguchi, K., Hoshino, M., et al. (2013). Anti-stress effect of theanine on students during pharmacy practice: Positive correlation among salivary ?-amylase activity, trait anxiety and subjective stress. Pharmacology Biochemistry and Behavior, 111, 128-135.

van Geijlswijk, I. M., Korzilius, H. P., & Smits, M. G. (2010). The use of exogenous melatonin in delayed sleep phase disorder: A meta-analysis. Sleep, 33(12), 1605-1614.

van Tiggelen, C., Peperkamp, J., & Tertoolen, H. (1984). Assessment of vitamin B12 status in CSF. American Journal of Psychiatry, 141(1), 136-137.

Vaucher, P., Druais, P., Waldvogel, S., & Favrat, B. (2012). Effect of iron supplementation on fatigue in nonanemic menstruating women with low ferritin: A randomized controlled trial. Canadian Medical Association Journal, 184(11), 1247-1254.

Verdon, F., Burnand, B., Stubi, C. F., Bonard, C., Graff, M., Michaud, A., et al. (2003). Iron supplementation for unexplained fatigue in non-anaemic women: Double blind randomised placebo controlled trial. British Medical Journal, 326(7399), 1124.

Ward, M. W., & Holimon, T. D. (1999). Calcium treatment for premenstrual syndrome. Annals of Pharmacotherapy, 33(12), 1356-1358.

Washburne, A. C. (1950). Nicotinic acid in the treatment of certain depressed states: A preliminary report. Annals of Internal Medicine, 32(2), 261-269.

Wass, C., Klamer, D., Katsarogiannis, E., Pålsson, E., Svensson, L., Fejgin, K., et al. (2011). L-lysine as adjunctive treatment in patients with schizophrenia: A single-blinded, randomized, cross-over pilot study. BMC Medicine, 9(1), 40.

Whitaker, R. (2005). Anatomy of an epidemic: Psychiatric drugs and the astonishing rise of mental illness in America. Ethical Human Psychology and Psychiatry, 7(1), 23-35.

Wood, D., Reimherr, F., & Wender, P. (1984). Amino acid precursors for the treatment of attention deficit disorder, residual type. Psychopharmacology Bulletin, 21(1), 146-149.

Wright, J. V. (1992). Treatment of chronic anxiety and

associated physical complaints with niacinamide and essential fatty acids: Two cases. Journal of Orthomolecular Medicine, 7(3), 182-186.

Wyatt, K., Dimmock, P., & Jones, P. (2000). Poor-quality studies suggest that vitamin B6 use is beneficial in premenstrual syndrome. Western Journal of Medicine, 172(4), 245.

Yamada, N. (1995). Treatment of recurrent hypersomnia with methylcobalamin (vitamin B12): A case report. Psychiatry and Clinical Neurosciences, 49(5?6), 305-307.

Yamatsu, A., Yamashita, Y., Maru, I., Yang, J., Tatsuzaki, J., & Kim, M. (2015). The improvement of sleep by oral intake of GABA and apocynum venetum leaf extract Journal of Nutritional Science and Vitaminology, 61(2), 182-187.

Yoto, A., Motoki, M., Murao, S., & Yokogoshi, H. (2012). Effects of L-theanine or caffeine intake on changes in blood pressure under physical and psychological stresses. *Journal of physiological anthropology,* 31(1), 1.

Yoto, A., Murao, S., Motoki, M., Yokoyama, Y., Horie, N., Takeshima, K., et al. (2012). Oral intake of ?-aminobutyric acid affects mood and activities of central nervous system during stressed condition induced by mental tasks. *Amino acids,* 43(3), 1331-1337.

Zanardi, R., & Smeraldi, E. (2006). A double-blind, randomised, controlled clinical trial of acetyl-L-carnitine vs. amisulpride in the treatment of dysthymia. *European Neuropsychopharmacology,*16(4), 281-287.

Zeinoddini, A., Ahadi, M., Farokhnia, M., Rezaei, F., Tabrizi, M., & Akhondzadeh, S. (2014). L-lysine as an adjunct to risperidone in patients with chronic schizophrenia: A double-blind, placebo-controlled, randomized trial. *Journal of Psychiatric Research,* 59, 125-131.

Zhdanova, I. V., & Piotrovskaya, V. R. (2000). Melatonin treatment attenuates symptoms of acute nicotine withdrawal in humans. *Pharmacology Biochemistry and Behavior,* 67(1), 131-135.