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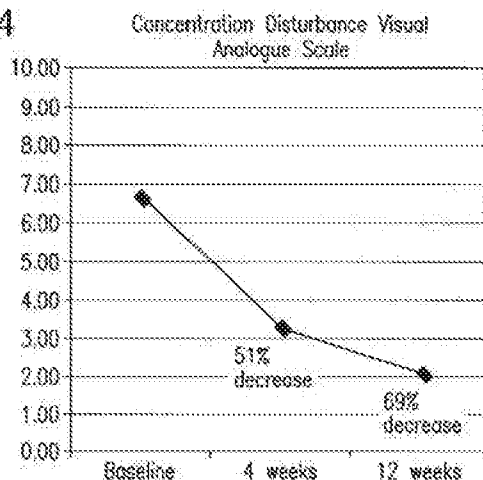
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(54) Title: COMPOSITIONS AND METHODS FOR TREATMENT OF NEUROPSYCHOLOGICAL DEFICITS

FIG. 4



(57) Abstract: Pharmaceutical compositions and methods for the treatment of neuropsychological impairment in human patients comprising a central nervous system (CNS) stimulant in a daily low-dosage amount, and a micronutrient composition containing acetyl L-carnitine, L-tyrosine, N-acetyl cysteine, and alpha-lipoic acid. The CNS stimulant and micronutrient components may be in admixture for convenient daily oral administration of a low dosage CNS stimulant and micronutrients in the range of about 60 - 250 mg acetyl L-carnitine, 50-200 mg L-tyrosine, 60 -250 mg N-acetyl cysteine, and 25 - 100 mg alpha-lipoic acid per day.

COMPOSITIONS AND METHODS FOR TREATMENT OF NEUROPSYCHOLOGICAL DEFICITS

[0001] This application is a continuation-in-part of U.S. Patent Application Serial No. 13/530,673, filed June 22, 2012, which claims the benefit of U.S. Provisional Application Serial No. 61/500,869, filed June 24, 2011.

FIELD OF THE INVENTION

[0002] This disclosure relates to pharmaceutical compositions and methods for the treatment of neuropsychological deficits including concentration disturbances and decreased alertness, which are symptoms of traumatic brain injury, encephalopathy conditions, multiple strokes, post-CVA, Alzheimer's disease, and other disorders such as chronic fatigue syndrome and fibromyalgia in which decreased alertness, poor concentration, and cognitive decline are a major symptom. In particular, provided herein are pharmaceutical compositions and treatment regimes utilizing a combination of a low dose central nervous system (CNS) stimulant with a group of high potency nutrients, the strategic combination of which provides significantly improved outcomes for patients experiencing neuropsychological impairment.

BACKGROUND

[0003] Various traumatic and physiological conditions give rise to neuropsychological impairment, marked by deficits in alertness and increases in concentration disturbances. Multiple concussions, repeated sub-concussions, and mild to severe traumatic brain injury (TBI), physical injury-induced encephalopathic syndromes, as well as metabolic, alcoholic, or hepatic encephalopathies, are particularly symptomatic for difficulties in maintaining concentration and alertness.

[0004] Individuals who have suffered a concussive blow to the head, face, neck (or anywhere on the body with an associated impulsive force, severe acceleration, or severe deceleration, of the head (e.g., whiplash)), such as occur in military blasts or explosions,

motor vehicle accidents, and in contact sports (football, boxing, hockey, etc.) can suffer a variety of neuropsychological impairments, including inability to focus attention or concentrate, and inability to remain alert. Post-concussion syndrome (PCS) is recognized as a common sequelae of mild, moderate, and severe TBI, as well as from whiplash and similar injuries which may or may not have given rise to any loss of consciousness. Thirty to eighty percent of patients with mild to moderate TBI experience PCS, including deficits in neuropsychological function, particularly deficits in alertness, concentration, memory, processing speed, and reaction time.

[0005] About 1.75 million people sustain TBI in the United States every year. (Centers for Disease Control and Prevention. Injury Prevention & Control: Traumatic Brain Injury. Traumatic Brain Injury. Available at: <http://www.cdc.gov/TraumaticBrainInjury/index.html>). Ten percent of Army infantry soldiers having served one-year deployment in Iraq report injuries with associated altered consciousness; these injuries typically involve concussive impacts, blasts, or explosions. (Hoge CW, McGurk D, Thomas JL, et al. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med* 2008; 358:453). Moreover, patients with disabling symptoms of PCS that persist after several months are often more disabled than they were immediately after the initial trauma or injury.

[0006] In the sport of boxing, chronic TBI is recognized as a common occurrence and termed "dementia pugilistica." In reports of the National Football League, players with a history of multiple concussions and resulting neuropsychological deficits are labeled with "chronic traumatic encephalopathy" (CTE). Such boxers and football players report a variety of neuropsychological impairments, including inability to focus attention, inability to remain alert, disorientation, confusion, slowed muscular movements, staggered gait, and impeded speech.

[0007] CFS, also known as Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS) or Myalgic Encephalomyelitis (ME), is another disorder characterized by attention deficit and concentration disturbances with overwhelming fatigue of greater than six months

duration that is not improved by rest and may be worsened by physical or mental activity. Patients with CFS typically function at a significantly lower level of activity than they were capable of before the onset of illness.

[0008] CFS patients commonly report various symptoms including weakness, muscle pain, post-exertional fatigue lasting more than 24 hours, impaired memory and/or mental concentration, impaired alertness, depression, and insomnia. These symptoms are often made worse by being tired and in pain the majority of one's waking hours. The immune system is frequently dysfunctional in patients experiencing chronic fatigue syndrome, and consequently many patients with CFS also experience frequent sore throats, colds, and flu-like symptoms. Benign lymphadenopathy can also occur in some patients. Other commonly observed symptoms of CFS include: abdominal pain, alcohol intolerance, bloating, chest pain, headaches, chronic cough, diarrhea, dizziness, dry eyes or mouth, ear aches, irregular heartbeat, jaw pain, morning stiffness, nausea, night sweats, psychological problems (depression, irritability, anxiety, and/or panic attacks), shortness of breath, skin sensations such as tingling, and weight loss.

[0009] The cause or causes of CFS have not been identified. CFS is a profoundly multifactorial condition. However, its myriad symptoms profile has been traced to a disintegration of neurologic, endocrine, and immune system cooperation, possibly attenuated by dysfunction of the hypothalamic-pituitary-adrenal hormonal axis.

[0010] To be diagnosed with CFS, patients typically satisfy two criteria: (1) significant to severe fatigue for at least six months (herein referred to as "chronic fatigue"), with other known medical conditions (whose manifestation can include fatigue) having been excluded by clinical diagnosis; and (2) concurrently four or more of the following symptoms: post-exertional malaise, impaired memory or concentration, unrefreshing sleep, muscle pain, multiple joint pains without redness or swelling, tender cervical or axillary lymph nodes, sore throat, and headache, such symptoms having persisted or recurred during six or more consecutive months of illness and not having predated the fatigue. It has been estimated that about 1% of the population in the United States has been diagnosed with CFS.

[0011] No prescription drugs have been developed specifically for CFS. The symptoms usually vary considerably over time and among patients. These factors can complicate the treatment process and typically require patients and health care professionals to constantly monitor and revise their treatment strategies. Current therapies for treating CFS primarily focus on attempts at relieving the most debilitating symptoms (i.e., pain, insomnia, and depression). Currently there are no United States Food and Drug Administration ("FDA")-approved or generally accepted treatments that significantly improve or cure CFS.

[0012] Similarly, "fibromyalgia" is a condition that includes an overlapping list of symptoms with CFS and frequently includes fatigue, chronic musculoskeletal pain, chronic flu-like symptoms, depression, neuropsychological impairment, and cognitive dysfunction. Fibromyalgia is predominately characterized by widespread muscular pains and fatigue.

[0013] Fibromyalgia also is characterized by abnormal pain processing, sleep disturbances, chronic fatigue, and is often accompanied by significant psychological distress. Patients experiencing fibromyalgia may also have other symptoms, including morning stiffness, tingling or numbness in the hands and feet, headaches, including migraines, irritable bowel syndrome, problems with thinking and memory (sometimes called "brain fog"), painful menstrual periods, and other pain syndromes. The prevalence of fibromyalgia in the United States is estimated at 2%, affecting 5 million adults in 2005. The prevalence is much higher among women than men (3.4% versus 0.5%) (Female: Male ratio 7:1).

[0014] Lyrica (pregabalin capsules) is approved by the FDA for the treatment of fibromyalgia. Fibromyalgia also is commonly treated with a variety of drugs developed and approved for other purposes, such as analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), antidepressants, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), mixed reuptake inhibitors, and benzodiazepines.

[0015] Chronic fatigue may also be caused by other medical conditions. These include, among others, cancer, AIDS, chronic hepatitis B & C, autoimmune disorders, Lyme's disease, Parkinson's disease, Alzheimer's disease, psychological disorders including depression, attention deficit disorder (ADD), and attention deficit hyperactivity disorder

(ADHD), multiple sclerosis, sickle cell anemia, and congestive heart failure. In the United States, 24% of the general population has had fatigue lasting 2 weeks or longer; 59%-64% of these persons report that their fatigue has no identifiable medical cause. In one study, 24% of patients in primary care clinics reported having prolonged fatigue (>1 month). In many persons with prolonged fatigue, the fatigue persists beyond 6 months and has no identifiable medical cause.

[0016] Accordingly, a significant need exists for compositions and methods for the treatment of conditions in which decreased alertness, poor concentration, and cognitive decline are a problem. The present disclosure is intended to satisfy this need and is believed to provide significant advantages in patient health care.

SUMMARY

[0017] The compositions and treatment regimes discussed herein comprise a combination of a low dose central nervous system (CNS) stimulant with a highly-potent group of four specific nutrients for the treatment of neuropsychological impairment manifested by deficits in attention and/or alertness as a result of TBI, PCS, CFS, CTE, or other encephalopathy conditions, such as metabolic, alcoholic, or hepatic encephalopathy, multiple strokes, post-CVA, Alzheimer's disease, and other conditions and disorders in which decreased alertness, poor concentration, and cognitive decline are a problem (hereinafter referred to as "neuropsychological impairment"). The compositions and methods are believed to provide significantly better short and long term patient outcomes than the use of current treatment regimes.

[0018] In one aspect, the present disclosure provides compositions for the treatment of neuropsychological impairment, such compositions including a central nervous system stimulant in a therapeutically effective low-dosage amount, about 60 to 250 mg acetyl L-carnitine, about 50 to 200 mg L-tyrosine, about 60 to 250 mg N-acetyl cysteine, and about 25 to 100 mg alpha-lipoic acid.

[0019] In another aspect, the present disclosure provides methods for treating such neuropsychological impairment in a human patient by administering a daily low-dosage amount of a central nervous system stimulant and therapeutically effective daily dosages of acetyl L-carnitine, L-tyrosine, N-acetyl cysteine, and alpha lipoic acid. In a preferred embodiment, the daily administration includes about 350 mg to 1400 mg L-tyrosine; and an antioxidant micronutrient component of about 250 mg to 1250 mg N-acetyl cysteine, and about 150 mg to 600 mg alpha-lipoic acid.

[0020] In yet another aspect, the present invention provides methods of treating neuropsychological impairment in a human patient by orally administering on a daily basis a central nervous system stimulant in a low-dosage amount, about 100 mg to 2000 mg acetyl L-carnitine, about 1000 mg to 2000 mg L-tyrosine; about 100 mg to 2000 mg N-acetyl cysteine, and about 50 mg to 1000 mg alpha-lipoic acid. The micronutrient antioxidant component may further comprise, for example, L-aurine (such as, about 50 to 1000 mg, 100 to 500 mg, or 200 to 400 mg).

[0021] The central nervous system stimulant may be any suitable CNS medication, including, but not limited to, methylphenidate, dexamethylphenidate, modafinil, armodafinil, amphetamines, and atomoxetine HCl, among others, so long as a therapeutically effective low dosage amount is provided as discussed herein, and as may be determined by one of skill in the art given the examples and teachings provided by way of illustration herein.

[0022] In one aspect, the compositions and treatment methods utilize a low dosage amount of CNS medicament, together with therapeutically effective amounts of acetyl L-carnitine, L-tyrosine, N-acetyl cysteine, and alpha-lipoic acid, combined together in a pill, capsule, tablet, or liquid dosage form for oral ingestion. For example, for methylphenidate HCl the composition of one pill, tablet or capsule would typically contain about 0.75 to 7.5 mg, 1.25 to 5 mg, or 2 to 3 mg methylphenidate HCl, but may contain other amounts of methylphenidate HCl. Similarly for modafinil or armodafinil, the composition of one pill would typically contain about 4 to 40 mg, 6 to 25 mg, or 10 to 20 mg modafinil or armodafinil, but may contain other amounts. For dexamethylphenidate HCl the composition

of one pill would typically contain about 0.5 to 5 mg, 0.6 to 3 mg, or 0.2 to 2 mg, but may contain other amounts of dexamethylphenidate HCl. For amphetamines, the composition of one pill would typically contain 1 to 10 mg, 1.2 to 6 mg, or 0.4 to 4 mg amphetamines, but may contain other amounts. For atomoxetine HCl the composition of one pill would typically contain 2 to 20 mg, 3 to 18 mg, or 5 to 10 mg, but may contain other amounts of atomoxetine HCl. For caffeine the composition of one pill would typically contain about 15 to 200 mg, 30 to 125 mg, or 50 to 100 mg, but may contain other amounts of caffeine. Such compositions may also be provided, or administered simultaneously, with a broad-spectrum multivitamin and multimineral supplement, or in admixture therewith in a dosage form for ingestion on a daily basis to cure or significantly mitigate neuropsychological impairment.

[0023] The preferred embodiments rely, at least in part, on relatively low doses of a CNS stimulant medication. No study to date has shown that CNS stimulant intervention can produce a sustained beneficial effect on the long-term experience and prognosis for patients suffering with neuropsychological impairment. Further, even when medications are successfully prescribed to address certain symptoms, the vast majority of patients achieve less than complete improvement with regular relapses of the condition being the norm.

[0024] When the cells of the nervous, endocrine, and immune systems become depleted of energy after prolonged periods of stress, trauma, and/or infection, a disruption of the balance among these systems can occur. This disruption of neurologic, endocrine, and immune system cooperation (possibly attenuated by dysfunction of the hypothalamic-pituitary-adrenal hormonal axis) is believed to be the prevailing etiology of CFS. The resulting symptom profiles almost always contain a significant level of chronic fatigue and/or chronic pain, and often vary from patient to patient.

DESCRIPTION OF DRAWINGS

[0025] Figure 1 illustrates patient fatigue as measured by Checklist Individual Strength (CIS) over time according to one aspect of the compositions and methods disclosed herein.

[0026] Figure 2 illustrates patient fatigue as measured by Visual Analogue Scale (VAS) over time according to one aspect of the compositions and methods disclosed herein.

[0027] Figure 3 illustrates patient fatigue and concentration disturbances as measured by CIS over time according to one aspect of the compositions and methods disclosed herein.

[0028] Figure 4 illustrates patient concentration disturbances as measured by VAS over time according to one aspect of the compositions and methods disclosed herein.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[0029] Provided herein are compositions and methods utilizing a low dosage of a CNS stimulant in combination with certain high-potency micronutrients. The high potency micronutrient components provide the cellular fuel (amino acids, antioxidants, and mitochondrial cofactors) that enable the nervous, endocrine, and immune system cells to rebuild and reintegrate into a functional neuro-endocrine-immune axis, while the low-dose CNS stimulant provides the necessary catalyst (i.e., spark) to enhance and fuel this process over time. In other words, the high-potency micronutrient components support and enhance the functioning of the nervous, immune, and endocrine systems to a level at which the drug is able to produce its positive clinical effect on the neuropsychological symptoms without causing further depletion or degradation of these systems.

[0030] It is believed that the specific combined micronutrients and amounts discussed herein together with the low dose CNS stimulant medication have synergistic effects and provoke a reintegration of the nervous, endocrine, and immune systems in a significant number of patients with neuropsychological disorders, significantly diminishing or mitigating symptoms, and allowing at least a significant subset of patients to return to and/or maintain functional work status.

[0031] With regard to the CNS stimulant component of the compositions and treatment methods herein, in most cases using the manufacturer's recommended dosage range

of a CNS stimulant will not be successful and/or will be detrimental for the long-term treatment of patients.

[0032] Particular examples of suitable CNS medications that may be used herein include, but are not limited to, methylphenidate HCl (e.g., Ritalin[®], Daytrana[®], CONCERTA[®], Metadate[®], Methylin[™]), dexamethylphenidate HCl (e.g., FOCALIN[®]), modafinil (e.g., PROVIGIL[®]), armodafinil (e.g., NUVIGIL[®]), amphetamines (e.g., ADDERALL[®], Vyvanse[®]), guanfacine (e.g., Intuniv[™]), atomoxetine HCl (e.g., Strattera[®]), and pharmaceutically acceptable salts and derivatives thereof. It should be noted, however, that other central nervous system stimulants may be selected and used according to the teachings, compositions, and methods discussed herein, including, but not limited to, lisdexamfetamine, phentermine, dexamphetamine, dextroamphetamine, pemoline, and caffeine, as well as pharmaceutically acceptable salts and derivatives thereof.

[0033] Therapeutically effective dosages of CNS medications for use herein are generally low dosages of the CNS medication. "Low dosage" amount of the CNS medication means a dose of between about 10% to 75%, 15% to 60%, 20% to 50%, or less of the manufacturer's suggested starting dosage. The preferred dose is, in most cases, 50% or less than the manufacturer's recommended dosage (MRD). According to one aspect, illustrative low oral dosage amounts of CNS medications for use herein are provided in Table 1 below.

TABLE 1

1. Methylphenidate HCl (e.g., Ritalin[®], Daytrana[®], CONCERTA[®], Metadate[®], Methylin[™])

• **2.5mg – 40mg per day**

(18mg – 72mg per day is the Manufacturer's recommended dosage range)

2. Modafinil (e.g., PROVIGIL[®])

• **30mg – 100mg per day**

(200mg – 400mg per day is the Manufacturer's recommended dosage range)

3. Armodafinil (e.g., NUVIGIL[®])

• **20mg – 100mg per day**

(150mg – 250mg per day is the Manufacturer's recommended dosage range)

4. Dexmethylphenidate HCl (e.g., FOCALIN[®])

• **2.5mg – 10mg per day**

(5mg – 20mg per day is the Manufacturer's recommended dosage range)

5. Amphetamines (e.g., ADDERALL[®], Vyvanse[®])

• **2.5mg – 20mg per day**

(5mg – 40mg per day is the Manufacturer's recommended dosage range)

6. Atomoxetine HCl (e.g., Strattera[®])

• **20mg – 50mg per day**

(40mg – 100mg per day is the Manufacturer's recommended dosage range)

7. Caffeine

* 50mg – 500mg per day

[0034] In one aspect, the CNS medication is administered in oral dosage amounts of about 2.5 to 40 mg/day methylphenidate, about 5 to 20 mg/day methylphenidate, or about 10 to 20 mg/day methylphenidate. In another aspect, the CNS medication is administered in amounts of about 30 to 100 mg/day modafinil, about 30 to 50 mg/day modafinil, or about 40 to 50 mg/day modafinil. In another aspect, the CNS medication is administered in amounts of about 20 to 80 mg/day armodafinil, about 20 to 40 mg/day armodafinil, or about 30 to 40 mg/day armodafinil. In yet another aspect, the CNS medication is administered in amounts of about 2.5 to 10 mg/day dexamethylphenidate, about 2.5 to 5 mg/day dexamethylphenidate, or about 3.5 to 5 mg/day dexamethylphenidate. In yet another aspect, the CNS medication is administered in amounts of about 2.5 to 20 mg/day amphetamine, about 2.5 to 10 mg/day amphetamine, or about 5 to 10 mg/day amphetamine. In yet a further aspect, the CNS medication is administered in amounts of about 20 to 50 mg/day atomoxetine, about 20 to 25 mg/day atomoxetine, or about 22.5 to 25 mg/day atomoxetine, or about 50 to 500 mg/day caffeine, 100 to 400 mg/day caffeine, or about 100 to 300 mg/day caffeine. Two or multiple CNS stimulants can also be included in the same composition or method and the amounts reduced proportionally.

[0035] With regard to the nutrient components, these include various components, each of which may be categorized as having particular functions in the treatment regime. A first component is micronutrients that stimulate energy production; while not wishing to be bound by theory, we believe that these nutrient stimulants help the CNS drug operate more effectively at the low dosages provided for herein. The second component is micronutrients that provide for a “balanced cooling system” for cells; these micronutrients appear to decrease total free radical load and oxidative stress levels, thus reducing the potential for toxic or other side effects of the CNS medication.

[0036] Preferred nutrients for energy production according to the teachings herein include acetyl-L-carnitine and L-tyrosine. In some cases, the energy stimulating micronutrient component may further include vitamin B6 (pyridoxine), and vitamin B12 (methylcobalamin). Preferred nutrients that provide for a restorative and balancing effect include N-acetyl-cysteine, alpha-lipoic acid, and optionally L-aurine. In some cases, the antioxidant micronutrient component may further include vitamin C, vitamin E, and beta-carotene. Other nutrients that provide for a restorative and balancing effect and may optionally be included are zinc and selenium, among others.

[0037] Additional optional vitamins and nutrients include mixed tocopherols, vitamin B1 (thiamine), vitamin B2 (riboflavin), niacinamide, calcium pantothenate, choline (bitartrate), inositol, folic acid (folacin), folinic acid, biotin, vitamin D3 (cholecalciferol), calcium, magnesium, iron, iodine, copper, manganese, potassium, chromium, molybdenum, and/or boron.

[0038] Thus, the high potency nutrient components suitable for use herein include therapeutically effective amounts of two or more nutrients for energy stimulation (collectively, the "micronutrient stimulant component") and two or more nutrients for decreasing free radical load and oxidative stress levels (collectively, the "micronutrient antioxidant component"). The preferred combinations of nutrient components include, in amounts as discussed herein, at least acetyl-L-carnitine and L-tyrosine for energy production, and N-acetyl-cysteine together with alpha-lipoic acid and, optionally, L-aurine, for decreasing oxidative stress. Other incidental nutrients may include, for example, various high potency vitamins, minerals, amino acids, antioxidants, cofactors, free radical scavengers, elements or biochemical compounds as discussed hereinbelow.

[0039] Suitable daily oral dosages of micronutrients include, for example, acetyl L-carnitine in amounts of about 100mg to 2000mg, L-tyrosine in amounts of about 100mg to 2000mg, N-acetyl cysteine in amounts of about 100mg to 2000mg, and alpha-lipoic acid in amounts of about 50mg to 1000mg, and optionally L-aurine, in amounts of about 50mg to 1000mg. Other suitable amounts include acetyl L-carnitine in amounts of about 400mg to

1600mg, L-tyrosine in amounts of about 350mg to 1400mg, N-acetyl cysteine in amounts of about 250mg to 1250mg, and alpha-lipoic acid in amounts of about 150mg to 600mg; or acetyl L-carnitine in amounts of about 800mg to 1200mg, L-tyrosine in amounts of about 700mg to 1500mg, N-acetyl cysteine in amounts of about 500mg to 750mg, and alpha-lipoic acid in amounts of about 300mg to 450mg.

[0040] In another aspect, suitable amounts of micronutrients for single unit oral dosage forms include, for example, acetyl L-carnitine in amounts of about 100mg to 150mg, L-tyrosine in amounts of about 80mg to 100mg, N-acetyl cysteine in amounts of about 100mg to 150mg, alpha-lipoic acid in amounts of about 40mg to 60mg, and optionally L-tyrosine in amounts of about 40mg to 60mg. In another case, suitable dosage amounts include acetyl L-carnitine in amounts of about 90mg to 190mg, L-tyrosine in amounts of about 70mg to 150mg, N-acetyl cysteine in amounts of about 90mg to 190mg, and alpha-lipoic acid in amounts of about 35mg to 75mg; or acetyl L-carnitine in amounts of about 60mg to 250mg, L-tyrosine in amounts of about 50mg to 200mg, N-acetyl cysteine in amounts of about 60mg to 250mg, and alpha-lipoic acid in amounts of about 25mg to 100mg. Optional amounts of L-tyrosine for such dosage forms include, for example, 35mg to 75g, or 25mg to 100mg L-tyrosine.

[0041] Illustrative dosages of micronutrients for use herein also include, for example, acetyl L-carnitine in amounts of about 1mg/day/kg to 27mg/day/kg, L-tyrosine in amounts of about 1mg/day/kg to 27mg/day/kg, N-acetyl cysteine in amounts of about 1mg/day/kg to 27mg/day/kg, alpha-lipoic acid in amounts of about 0.5mg/day/kg to 14mg/day/kg, and optionally L-tyrosine, in amounts of about 0.5mg/day/kg to 14mg/day/kg. Other suitable dosages of micronutrients, include, for example, acetyl L-carnitine in amounts of about 5mg/day/kg to 23mg/day/kg, L-tyrosine in amounts of about 5mg/day/kg to 20mg/day/kg, N-acetyl cysteine in amounts of about 3mg/day/kg to 18mg/day/kg, and alpha-lipoic acid in amounts of about 2mg/day/kg to 9mg/day/kg; or acetyl L-carnitine in amounts of about 11mg/day/kg to 18mg/day/kg, L-tyrosine in amounts of about 10mg/day/kg to 15mg/day/kg, N-acetyl cysteine in amounts of about 7mg/day/kg to 11mg/day/kg, and alpha-lipoic acid in amounts of about 4mg/day/kg to 7mg/day/kg.

[0042] The nutrient compositions, together with a low dose CNS medication, may also be provided together with a general daily multivitamin and multimineral supplement, for example, as shown in Table 2 below.

TABLE 2

ONE (1) Illustrative Tablet Contains:**Typical Dosage Range: 1-8 tablets per day****Antioxidant Amino Acids**

N-Acetyl Cysteine 125 mg

Alpha Lipoic Acid 50 mg

Stimulant Amino Acids

Acetyl L-Carnitine 125 mg

L-Tyrosine 100 mg

Low-Dose Pharmaceutical**Stimulant**

Methylphenidate USP 2.5 mg

Optional Antioxidant Amino Acid

L-Taurine 50 mg

Optional Multivitamin Supp.:

Beta-Carotene 1,250 IU

Vitamin C 125 mg

Vitamin E (total Vit. E) 50 IU

Vitamin B-1 (Thiamine) 7.5 mg

Vitamin B-2 (Riboflavin) 7.5 mg

Vitamin B-6 (Pyroxidine) 15 mg

Niacinamide 7.5 mg

Calcium Pantothenate 7.5 mg

Choline (Bitartrate) 7.5 mg

Inositol 7.5 mg

Folic Acid 100 mcg

Biotin 100 mcg

Vitamin D3 (Cholecalciferol) 250 IU

Vitamin B12 (Methylcobalamin) 250 mcg

Optional Multimineral Supp.:

Calcium 25 mg

Magnesium 12.5 mg

Iron 2.25 mg

Iodine 18.75 mcg

Copper 0.25 mg

Manganese 1.25 mg

Zinc 3.75 mg

Selenium 25 mcg

Chromium 12.5 mcg

Molybdenum 37.5 mcg

Potassium 12.5 mg

Boron 0.25 mg

[0043] As used herein, the term "nutrient" is intended to include either or both micronutrients and macronutrients. Micronutrients can include organic compounds or chemical elements required for biochemical and physiological processes. Such organic compounds and chemical elements may include, for example, vitamins, minerals, amino acids, antioxidants, cofactors, free radical scavengers, or other biochemical compounds that are utilized for the maintenance, regulation or function of biochemical and physiological processes. Macronutrients can include organic compounds and chemical elements which are required in relatively large amounts for biochemical and physiological processes of an animal. Specific examples of macronutrients include protein, carbohydrates, and fat.

[0044] The term "vitamin" herein means a micronutrient that acts generally in small amounts in the regulation of various metabolic processes but generally does not serve as an energy source or as a building unit. Vitamins are ordinarily ingested on a regular basis or stored in quantity in humans due to deficiencies in biosynthetic capacity. Specific examples of optional vitamin micronutrients that may be particularly useful together with the compositions and methods herein include vitamins A, B, C, D and E.

[0045] The term "mineral" herein means naturally occurring homogeneous or apparently homogeneous and generally solid crystalline chemical elements or compounds that result from inorganic processes of nature having a characteristic crystal structure and chemical composition. Specific examples of optional mineral and chemical element micronutrients that may be particularly useful together with the compositions and methods herein include zinc, selenium, iron, iodine and boron.

[0046] The term "antioxidant" herein means a substance that opposes oxidation or inhibits reactions promoted by, for example, oxygen, peroxides, or free radicals. Specific examples of additional antioxidant micronutrients useful together with the compositions and methods herein include vitamin C, bioflavonoid complex, vitamin E, vitamin B6, and beta-carotene. Specific examples of cofactor micronutrients useful together with the compositions and methods herein include vitamin B1, vitamin B2 and vitamin B6.

[0047] As used herein, the term "high potency" when used in reference to an antioxidant is intended to mean a non-vitamin or non-mineral antioxidant. The chemical or medicinal strength or the efficacy of such high potency antioxidants in the compositions herein can be, for example, greater in reducing oxidation, free radical destruction or chemical reactions induced by these chemical species, as compared to other antioxidants, or as compared to an amount of these same antioxidants as they are normally found in food. The chemical efficacy of the high potency antioxidants as they are used in the nutrient component herein is due to, for example, greater molar amounts of antioxidants or enhanced antioxidant effectiveness resulting from cooperative combinations with other antioxidants or nutrients in the formulations herein. The preferred high potency micronutrient antioxidants for use herein are N-acetyl cysteine and alpha lipoic acid. Examples of additional high potency antioxidants for use herein include L-taurine, coenzyme Q10, and/or glutathione.

[0048] The term "therapeutically effective amount" of a composition or component thereof refers to an amount that is effective for an intended therapeutic purpose. For example, in the context of treating neuropsychological impairment, a "therapeutically effective amount" is any amount that is effective in producing a significant positive effect on individuals suffering from decreased alertness, poor concentration, and/or cognitive decline, as demonstrated by the Example below. With regard to the CNS component of the disclosed compositions and methods, a "therapeutically effective amount" is a low dosage amount as defined hereinabove, or any amount sufficient to induce patient stimulation of alertness and decreased concentration disturbances without undue side effects when administered together with therapeutically effective amounts of the micronutrient stimulant and micronutrient antioxidant components, as disclosed herein. With regard to the micronutrient stimulants disclosed herein, a "therapeutically effective amount" is any amount sufficient to achieve patient stimulation of alertness and decreased concentration disturbances either alone or when administered together with therapeutically effective amounts of the CNS medicament and micronutrient antioxidant components, as disclosed herein. In the context of micronutrient antioxidants, a "therapeutically effective amount" is any amount sufficient to provide a decrease in free radicals and oxidative stress either alone or when administered in

combination with therapeutically effective amounts of the CNS medicament and micronutrient stimulant components, as disclosed herein.

[0049] Illustrative examples of therapeutically effective amounts are shown in Table 2 and the Example below. Therapeutically effective amounts of nutrients and CNS medications can also vary in range from the exemplary oral dosages shown herein by about 25% of the shown dosages up to and greater than about 200% of the dosages shown. In one case, the starting dosage may be 4 pills per day taken as 2 pills 2x/day – each pill having the nutrient composition shown in Table 2 and a corresponding low dosage amount of the daily CNS medication shown in Table 1. However, in patients who are extremely sensitive to taking prescription drugs or nutritional supplements, the effective dosage may be as low as one pill per day. For patients who do not respond to the starting dosage within 1-2 weeks, an increase in the treatment dosage may then be made to 6 pills per day (taken as 3 pill 2x/day) and, if necessary, to 8 pills per day (taken as 4 pills 2x/day – each pill having the composition shown in Table 2). Therefore, therapeutically effective amounts for oral dosages of one or more of the nutrients shown in Table 2 can be, for example, 30, 40, 50, 60, 70, 80, 90, 110, 120, 130, 140, 150, 160, 170, 180, 190 or greater than 200% of the amounts shown in Table 2. Effective amounts other than those exemplified above can be determined by those skilled in the art given the teachings and guidance provided herein.

[0050] In one case, the micronutrient components may further include a daily multivitamin/mineral supplement, which may be, for example, as shown in aspects of Table 2 above. Thus, the nutrient components may include a combination of vitamins, minerals, and high potency antioxidants. The nutrient components may include a combination of vitamin and mineral antioxidants, vitamin and high potency antioxidants, or mineral and high potency antioxidants. The nutrient components also may include various other combinations of these antioxidants and may contain, for example, one, two, three, four, five or more different antioxidants. Antioxidants are beneficial to physiological processes because they augment immune strength or physiological detoxification functions within cells and tissues. Moreover, multinutrient combinations are beneficial physiologically because of their interdependence in a variety of cellular processes. For example, mammalian mitochondria

are interdependent on multiple nutrients for healthful and efficient functioning. Administration of multinutrient antioxidant formulations can improve the functions dependent on such antioxidants as well as improve the functions dependent on the interplay of antioxidants with other nutrients such as vitamins and minerals. In some aspects, combinations of nutrients included as the nutrient compositions herein may include amounts or types of nutrients that together support the interdependent roles of two or more nutrients. A specific example of such interdependence is the ability of Vitamin C (ascorbate) to regenerate native Vitamin E (tocopherol) from its oxidized state as well as alpha lipoic acid to regenerate native Vitamin C (ascorbate) from its oxidized state.

[0051] N-acetyl-cysteine (NAC) is a nutrient with potent antioxidant activity. The acetyl moiety of the amino acid cysteine is a prevalent bioavailable oral source of glutathione. Glutathione is a potent antioxidant and component of the glutathione peroxidase enzyme system.

[0052] Alpha lipoic acid is a potent antioxidant found, for example, in the mitochondria. It acts as a coenzyme in the alpha-keto-dehydrogenase enzyme complex of the Krebs cycle to facilitate aerobic respiration as well as participates in the metabolic pathways which regenerate de novo levels of ascorbate, alpha-tocopherol, and glutathione. Alpha lipoic acid also functions as a potent free radical scavenger in both hydrophilic and hydrophobic cellular compartments.

[0053] Acetyl-L-carnitine is a stimulant nutrient (amino acid). It enriches the fuel mixture of the mitochondria. The acetyl moiety of the amino acid carnitine regulates fatty acid transport across the mitochondrial membrane. It enhances mitochondrial function and energy production by transporting additional fuel stores into the mitochondria during times of stress. It also functions to provide the mitochondria with a fuel source that enhances its ability to produce energy under anaerobic conditions. Anaerobic metabolism can occur, for example, when the electron transport chain is dysregulated due to a depletion of mitochondrial DNA.

[0054] L-tyrosine is one of the 20 amino acids that are used by cells to synthesize proteins. Tyrosine phosphorylation is considered to be one of the key steps in signal transduction and regulation of enzymatic activity. L-tyrosine is also a precursor to norepinephrine, a neurotransmitter that exerts a potent stimulating effect on the central nervous and endocrine systems.

[0055] Vitamin antioxidants that can be selected for inclusion in the micronutrient component herein include, for example, beta-carotene, vitamin C, vitamin E, vitamin B6 or vitamin B12. One or more of these or optional vitamin antioxidants can be included in the micronutrient component of the disclosed embodiments.

[0056] Beta-carotene is a vitamin antioxidant that also is convertible to vitamin A in the liver of animals. This class of nutrients includes all those defined by the term "retinoids" and includes those described as retinols. Since Vitamin A is only found in animal foods, beta-carotene provides about two thirds of the daily intake of retinoids in humans. Beta-carotene is converted to Vitamin A in both the gastrointestinal tract and the liver. Vitamin A is used by the body to enhance retinal function and night vision and also plays a role in the formation and maintenance of healthy epithelial tissue, which forms the body's primary barrier to infection.

[0057] Vitamin C, or ascorbic acid or ascorbate, is a strong reducing agent that can be reversibly oxidized to dehydroascorbic acid. The term vitamin C, as it is used herein, is intended to include any of several enolic lactones of keto aldonic acids that are stereoisomers of ascorbic acid. As described above, vitamin C functions in, for example, the Kreb's cycle and a deficiency can lead to scurvy. Vitamin C also functions in building and maintaining bone matrix, cartilage, dentin, collagen, and connective tissue in general. Furthermore, Vitamin C participates in resistance to infection by the immune system and proper adrenal gland function in reaction or resistance to stress.

[0058] Vitamin E, found in nature as mixed tocopherols, is a fat-soluble tocopherol complex with antioxidant properties. Vitamin E also plays a role in protecting cellular membrane fatty acids from oxidative damage. It is nutritionally required for mammals in

which its absence is associated with infertility, muscular dystrophy, or abnormalities in the vascular system. The term vitamin E, as it is used herein, is intended to include, any of the structurally similar chemical compounds found within the tocopherol family of organic compounds.

[0059] Vitamin B₆, or pyroxidine HCl or pyridoxine, is a water-soluble component of the vitamin B complex and plays a role in the proper formation and health of red blood cells and blood vessels, nerve function, gums, and teeth. In its active form, pyridoxalphosphate (B₆-PO₄) is a coenzyme involved in many types of transamination (amino acid metabolism) and decarboxylation reactions occurring in amino acid, carbohydrate, and fat metabolism. Vitamin B₆ also is a cofactor in immune system functioning. Although not generally considered to be an antioxidant, vitamin B₆ does exhibit antioxidant properties.

[0060] Vitamin B₁₂ (along with choline and folic acid) is a nutritional factor involved in transmethylation reactions. Vitamin B₁₂ is involved in the production of red blood cells and healthy nervous system functioning.

[0061] Mineral antioxidants that can be optionally selected for inclusion in the nutrient component herein include, for example, zinc or selenium. Either or both of these minerals as well as vitamin antioxidants may optionally be included in the micronutrient component of the disclosed embodiments.

[0062] Zinc, taken in the form of picolinate, carbonate, ascorbate, or complexed to a chelated amino acid, for example, is one mineral exhibiting antioxidant activity. Zinc also is utilized for the metabolic activity of about 200 or more enzymes and is considered important for cell division and the synthesis of DNA and polypeptides. Zinc deficiency contributes to growth retardation; even mild deficiency may limit growth in otherwise healthy children. Zinc functions, for example, in energy metabolism as part of the lactate dehydrogenase enzyme system. Zinc also participates in immune function, as evidenced by its role in promoting enhanced wound healing, and serves as an antioxidant as part of the superoxide dismutase enzyme system.

[0063] Selenium, taken in the form of picolinate, carbonate, ascorbate, or complexed to a chelated amino acid for example, is another mineral having antioxidant activity. Selenium is a component of the active sites of, for example, the enzymes glutathione peroxidase, iodothyronine 5'-deiodinase, and mammalian thioredoxin reductase. It is also present in several other mammalian selenoproteins. Both glutathione peroxidase and thioredoxin reductase catalyze reactions involved in the protection of cellular components against oxidative and free radical damage. Therefore, selenium as well as zinc augments the activity of enzymes within one or more antioxidant enzyme systems of an individual. Selenium also plays a role as a mammalian cell's second line of defense against damaging cell peroxides. It performs this role as an integral part of the glutathione peroxidase enzyme system.

[0064] Any of the nutrient antioxidants described above as well as others known in the art can optionally be included in the nutrient component of the compositions and methods herein. Additionally, other nutrients that function, for example, in one or more of the antioxidant enzyme systems described above or others also can be included.

[0065] Additional vitamins or minerals that can be included in the compositions and treatment regimes herein include additional vitamins, such as mixed tocopherols, vitamin B1 (thiamine), vitamin B2 (riboflavin), niacinamide, calcium pantothenate, choline (bitartrate), inositol, folic acid (folacin), biotin, or vitamin D3 (cholecalciferol), and/or additional minerals, such as calcium, magnesium, iron, iodine, copper, manganese, potassium, chromium, molybdenum, or boron. For example, one or more nutrients from the vitamin category can be additionally included. Similarly, one or more nutrients from the mineral category can be additionally included. Alternatively, one or more nutrients from both the vitamin and the mineral categories can be additionally included in the micronutrient component of the disclosed embodiments. Therefore, the micronutrient component of the disclosed embodiments can include any one or more, as well as all of the various combinations of the following vitamins or minerals: beta-carotene, vitamin C, vitamin E, vitamin B6, vitamin B12, zinc, selenium, mixed tocopherols, vitamin B1 (thiamine), vitamin B2 (riboflavin), niacinamide, calcium pantothenate, choline (bitartrate), inositol, folic acid

(folacin), biotin, vitamin D3 (cholecalciferol), calcium, magnesium, iron, iodine, copper, manganese, potassium, chromium, molybdenum, and/or boron.

[0066] Calcium is present in large amounts in the human body and is needed, for example, for structural integrity, blood clotting and nerve cell functioning. Calcium also is a mineral that is supportive and balancing to the nervous system and thus is particularly useful in some aspects of the compositions and methods disclosed herein.

[0067] Magnesium is involved in healthy intracellular metabolism of macromolecules such as carbohydrates and protein. A magnesium-ATP complex is the form of ATP used as a substrate in many biochemical reactions. Magnesium is a mineral that is supportive and balancing to the nervous system and thus is particularly useful in some aspects of the compositions and methods disclosed herein.

[0068] In another aspect, the present disclosure provides a pharmaceutical composition containing a combination of nutrients and/or one or more CNS medicaments, and optionally a pharmaceutically acceptable carrier. The compositions can be prepared by conventional methods known in the art. The term "pharmaceutically acceptable carrier" refers to any inactive substance that is suitable for use in a formulation for the delivery of the CNS stimulant and/or nutrients. A carrier may be an antiadherent, binder, coating, disintegrant, filler or diluent, preservative (such as antioxidant, antibacterial, or antifungal agent), sweetener, absorption delaying agent, wetting agent, emulsifying agent, buffer, and the like.

[0069] The pharmaceutical compositions may be in any suitable form, such as liquid, semi-solid, and solid dosage forms. Examples of liquid dosage forms include solution (e.g., injectable and infusible solutions), microemulsion, liposome, dispersion, or suspension. Examples of solid dosage forms include tablet, pill, capsule, microcapsule, and powder. A particular form of the composition suitable for delivering a CNS stimulant and nutrient compositions is a solid dosage form, such as a pill.

[0070] The compositions can be administered via any suitable enteral route or parenteral route of administration. Examples of enteral routes include oral, mucosal, buccal, and rectal route, or intragastric route. Examples of parenteral routes of administration include intravenous, intramuscular, intradermal, intraperitoneal, transtracheal, epidural and intrasternal, subcutaneous, or topical administration. The compositions can be administered using any suitable method, such as by oral ingestion, nasogastric tube, injection, infusion, implantable infusion pump, and osmotic pump.

[0071] In a preferred embodiment, the low-dose CNS stimulant medication and nutrient components are combined in a unit dosage form for oral ingestion (such as a pill, tablet, capsule, or liquid) in order to provide a safe and effective treatment. There is an intimate relationship between the medication and the nutrients, as the above-described dosing relationship between the key micronutrients (at least acetyl L-carnitine, L-tyrosine, N-acetyl cysteine, and alpha lipoic acid) and the CNS medication is beneficial to the success of the treatment. Thus, the CNS stimulant medication and nutrient compositions may be provided together in a single dosage form. This single dosage form ensures that patients are receiving the proper ratio of the nutrient compositions and the CNS medication. Thus, the CNS and nutrient components may be formulated as separate tablets or, more preferably, as a unitary combination tablet. The preferred pharmaceutical formulations are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the components is preferred. According to some aspects, patients may take, for example, from one to eight tablets per day as shown in Table 2, depending on their response to the treatment. In any event, in most instances, the CNS medication will be provided in daily low dosage amounts. The dosage forms may be administered once per day, twice, or multiple times per day, and continuing over a treatment period until symptoms disappear and/or significantly subside, typically 4 weeks, 8 weeks or 12 weeks, but also may continue as a prophylactic measure in the long term after symptoms have disappeared or significantly subsided, as determined by the attending physician.

[0072] While, in one case, a starting dosage for treatment of patients suffering neuropsychological impairment may be 2 tablets (Table 2), for example, twice per day, based

on each particular patient's response the dosage also may be changed, for example, to 4 pills, twice per day or to 1 pill, twice per day. It is to be understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the practitioner supervising administration of the compositions. Thus, while a patient may be started at one dose, that dose may be varied over time as the patient's condition changes.

[0073] The term "daily" means that the dosage is to be administered at least once daily. The frequency may be once daily, but also may be more than once daily, provided that any specified daily dosage is not exceeded.

[0074] The term "combination" means that the daily dosage of each of the CNS and the nutrient components is administered during the treatment day. As indicated above, it is particularly preferred that the components of the combination are administered at the same time; either as a unitary dosage form containing both components, or as separate dosage units. The components of the combination also may be administered at different times during the day, provided that the desired daily dosage is achieved.

[0075] In one aspect, it is preferable that there is no break in the treatment regimen during the treatment period. Thus, "continuous administration" of the CNS and nutrient combination means that the combination is administered at least once daily during the entire treatment period. Treatment periods may vary depending on the symptoms to be treated. Physician evaluation along with patient interaction will assist the determination of the duration of treatment. The dosage regimen may be indefinite, long term, short term, or treatments of a finite term, that may be less than 12 weeks, 8 weeks, or less than 4 weeks. It is anticipated that a patient may miss, or forget to take, one or a few dosages during the course of a treatment regimen, however, such patient is still considered to be receiving continuous administration.

[0076] Efficacy of the nutrient component correlates with purity level of the nutrients. Higher purity levels yield greater activity and, consequently, can allow a reduction in the amount included in one or more administrations.

[0077] The CNS medication and nutrients used with the compositions and methods herein preferably have a purity level greater than about 90%, more preferably greater than about 95%, and most preferably greater than about 98%. These higher purity levels can be obtained by methods well known in the art. Additionally, purity levels greater than about 98% and particularly greater than about 99% by total weight can be obtained by omitting fillers, binders or lubricants such as stearates or palmitates. Additionally, other substances which are known in the art to inhibit, or possibly inhibit, the absorption, bioavailability or tolerance of compounds in individuals also can be excluded from the formulations to achieve greater than about 98-99% purity without compromising the activity of the micronutrient component. However, it should be understood that such fillers, binders, lubricants or other substances also can be included when desirable. Given the teachings and guidance provided herein, those skilled in the art will know whether to utilize nutrient compositions less than the purity levels described above or to include additional substances and pharmaceutically acceptable excipients in a formulation. Accordingly, various formulations of pharmaceutically acceptable carriers known in the art for packaging and administration of nutrients or other administrable chemical compounds can be utilized in conjunction with the disclosed embodiments.

[0078] Nutrients for use in the formulations herein can be obtained from any of various sources known to those skilled in the art. For example, individual nutrients or combinations meeting the amounts or dosages exemplified herein can be produced by a commercial manufacturer. An exemplary commercial manufacturer is Enzymatic Therapy (Green Bay WI, and which can be found at the URL enzymatictherapy.com). Additionally, the nutrients can be purified biochemically or synthesized chemically using methods known to those skilled in the art.

[0079] The following example is intended to be illustrative and not limiting. Other CNS stimulants or combinations thereof may be used, as well as modifications of the dosing schedule and duration, and/or use of fewer or additional micronutrients, multivitamins and minerals, to maintain the appropriate standard of care for each set of patient circumstances.

EXAMPLE

[0080] A Phase IIa clinical trial was performed in Mill Valley, California. The results of this prospective, open-label 12-week clinical trial strongly demonstrated a significant positive effect on individuals suffering from chronic fatigue, decreased alertness, and concentration disturbances.

[0081] Objective: To investigate the effects of a nutrient-drug hybrid treatment utilizing a low-dose amphetamine derivative combined with a highly potent combination of micronutrients on fatigue, concentration disturbances, and quality of life in patients with Chronic Fatigue Syndrome (CFS).

[0082] Study design: A prospective, open label 12-week clinical trial in 15 patients who fulfill the 1994 CDC criteria for Chronic Fatigue Syndrome and have concentration difficulties. Study duration: 12 weeks. Eligibility criteria: The main eligibility criteria were male or female subjects who fulfill the 1994 CDC case definition for CFS, 18 to 65 years of age, and had subjective complaints of alertness and/or concentration deficits

[0083] Study intervention: Oral treatment was provided to 15 CFS patients consisting of a nutrient-drug hybrid containing the nutrients and dosages listed in Table 2 except that the methylphenidate and nutrients were delivered as separate pills. Treatment commenced with an initial dosage of 4 nutrient pills, plus methylphenidate 10 mg taken 1x/day. After 3 days of treatment, the study patients were contacted and, if they were tolerating the treatment without difficulty, the treatment dosage was increased to 4 nutrient pills, plus methylphenidate 10mg taken 2X/day. This dosage represents the nutrient and methylphenidate dosages shown in Table 2 which corresponds to a total of 8 pills per day (4 pills taken 2X/day).

[0084] The study treatment used the composition shown in Table 2, which includes the CNS medication, the four key nutrients, and a broad-spectrum multivitamin/mineral supplement to maintain patient standard of care (study patients had previously agreed not to ingest any supplemental nutrients, vitamins, or minerals, other than those provided during the study).

[0085] The primary outcome objective for this study was a clinically significant improvement in at least half the CFS patients. Clinically significant improvement is defined for the purposes of this study as an improvement of $\geq 33\%$ in either of the fatigue primary outcome measures. To date, no CFS treatment has shown this level of benefit.

[0086] Primary outcome measures: Three instruments were used to assess fatigue and concentration in accordance with established measurement techniques. See, e.g., Blockmans, D., et al., "Does Methylphenidate Reduce the Symptoms of Chronic Fatigue Syndrome?," *Am. J. of Medicine* (2006) 119, 167. e23-167. e30.

[0087] Two instruments were used to assess change in fatigue: (1) The Checklist Individual Strength (CIS) is a self-report questionnaire that assesses the severity of fatigue over the previous 2 weeks, ranking from 20 to 140. For the purposes of this study, we defined a clinically significant response as a 33% fall in fatigue scores or a score on the CIS ≤ 76 , which has been defined previously as the cut-off point for probable fatigue in employees. Patients fulfilling these criteria were considered responders. (2) A Visual Analogue Scale (VAS) measuring subjective fatigue was used as a second instrument (range 0 to 10).

[0088] Concentration disturbances were assessed with the concentration subscale of the CIS (5 items, range 5-35) on the one hand, and with a VAS (range 0-10) measuring subjective concentration on the other hand. Analogous to the CIS total score, significant clinical improvement was defined as a 33% fall of the concentration disturbances score on the CIS subscale.

[0089] Study Results - Primary Outcome Measures:

[0090] Fatigue: At the 4-week interim analysis, a clinically significant reduction in fatigue, as measured by a 33% or greater fall in the total CIS score, was present in 66% of the participants [10 of 15 responded significantly] with a mean fatigue symptom reduction of 33%. At the interim 12-week analysis, a clinically significant reduction in fatigue, as measured by a 33% or greater fall in the total CIS score, was present in 100% of the participants [7 of 7 patients responded significantly] with a mean fatigue symptom reduction

of 41% (see FIG. 1). The Visual Analogue Scale (VAS) showed similar results that were consistent with a clinically significant reduction in fatigue symptoms in 66% of the study patients [10 of 15 responded significantly] with a mean fatigue symptom reduction of 54% at 12-weeks (see FIG. 2).

[0091] Concentration disturbances: At the 4-week interim analysis, a clinically significant reduction in concentration disturbances, as measured by a 33% or greater fall in the concentration subscore of the CIS, was present in 66% of the participants [10 of 15 responded significantly] with a mean reduction in concentration disturbances symptoms of 36%. At the 12-week analysis, a clinically significant reduction in concentration disturbances symptoms, as measured by a 33% or greater fall in the concentration subscore of the CIS, was present in 85% of the participants [6 of 7 patients responded significantly] with a mean reduction in concentration disturbances symptoms of 50% at 12-weeks (see FIG. 3). The Visual Analogue Scale (VAS) showed similar results that were consistent with a clinically significant reduction in concentration disturbances symptoms in 80% of the study patients [12 of 15 responded significantly] with a mean reduction of concentration disturbances symptoms of 54% at 12-weeks (see FIG. 4).

[0092] Conclusions: Treatment with the nutrient-drug composition shown in Table 2 above and as described herein significantly improves fatigue, alertness and concentration disturbances in a majority of CFS patients. The nutrient-drug hybrid treatment used in this study was effective and well-tolerated.

[0093] All patents and publications cited herein are incorporated herein by reference. It should be readily understood that the invention is not limited to the specific examples and embodiments described and illustrated above. Rather, the examples and embodiments can be modified to incorporate any number of CNS drugs, nutrient components, dosing techniques and other variations, alterations, substitutions or equivalent arrangements not heretofore described, which are commensurate with the spirit and scope of the invention. For example, although the examples have been described with regard to certain preferred embodiments for carrying out the invention with regard to the treatment of CFS using low dose

methyphenidate, the invention may also be used for preparing compositions and treatment of neuropsychological impairment with other CNS drugs, as well as treatment of chronic fatigue and other conditions wherein decreased alertness and concentration deficits are major symptoms. Accordingly, the invention is not limited by the foregoing description, but is only limited by the scope of the appended claims.

CLAIMS

I claim:

1. An oral dosage composition for the treatment of neuropsychological impairment, comprising:

a central nervous system stimulant in up to a low-dosage amount;

60 to 250 mg acetyl L-carnitine;

50 to 200 mg L-tyrosine;

60 to 250 mg N-acetyl cysteine;

25 to 100 mg alpha-lipoic acid.
2. The composition of claim 1, wherein acetyl L-carnitine is present in a range of 90 to 190 mg.
3. The composition of claim 1, wherein acetyl L-carnitine is present in a range of 100 to 150 mg.
4. The composition of claim 1, wherein L-tyrosine is present in a range of 70 to 150 mg.
5. The composition of claim 1, wherein L-tyrosine is present in a range of 80 to 100 mg.
6. The composition of claim 1, wherein N-acetyl cysteine is present in a range of 90 to 190 mg.
7. The composition of claim 1, wherein N-acetyl cysteine is present in a range of 100 to 150 mg.
8. The composition of claim 1, wherein alpha-lipoic acid is present in a range of 35 to 75 mg.

9. The composition of claim 1, wherein alpha-lipoic acid is present in a range of 40 to 60 mg.
10. The composition of claim 1, further comprising about 25 to 100 mg L-taurine.
11. The composition of claim 10, wherein L-taurine is present in a range of 35 to 75 mg.
12. The composition of claim 1, wherein the central nervous system stimulant is atomoxetine HCl in an amount of about 2 mg to 20 mg.
13. The composition of claim 1, wherein the central nervous system stimulant is methylphenidate HCl in the amount of about 0.75 mg to 7.5 mg.
14. The composition of claim 1, wherein the central nervous system stimulant is dexamethylphenidate HCl in the amount of about 0.5 mg to 5 mg.
15. The composition of claim 1, wherein the central nervous system stimulant is modafinil in the amount of about 4 mg to 40 mg.
16. The composition of claim 1, wherein the central nervous system stimulant is armodafinil in the amount of 4 mg to 40 mg.
17. The composition of claim 1, wherein the central nervous system stimulant is an amphetamine in the amount of about 1 mg to 10 mg.
18. The composition of claim 1, further comprising one or more of vitamin B6 (pyridoxine) and vitamin B12.
19. The composition of claim 1, further comprising one or more of vitamin C, vitamin E, beta carotene, zinc and selenium.
20. The composition of claim 1, wherein the composition comprises acetyl L-carnitine, L-tyrosine, vitamin B6 (pyridoxine), vitamin B12, N-acetyl cysteine, alpha-lipoic acid, L-taurine, vitamin C, vitamin E and beta carotene.

21. The composition of claim 20, further comprising of one or more additional vitamins or minerals selected from the group consisting of zinc, selenium, mixed tocopherols, vitamin B1 (thiamine), vitamin B2 (riboflavin), niacinamide, calcium pantothenate, choline (bitartrate), inositol, folic acid (folacin), biotin, vitamin D3 (cholicaleiferol), calcium, magnesium, iron, iodine, copper, manganese, potassium, chromium, molybdenum and boron.

22. A method of treating neuropsychological impairment in a human patient comprising administering to the patient the composition of claim 1.

23. A method for treating neuropsychological impairment in a human patient comprising:
administering a daily low-dosage amount of a central nervous system stimulant and therapeutically effective daily dosages of acetyl L-carnitine, L-tyrosine, N-acetyl cysteine, and alpha lipoic acid.

24. The method of claim 23, wherein acetyl L-carnitine is administered in a range of about 100 to 2000 mg.

25. The method of claim 23, wherein acetyl L-carnitine is administered in a range of about 400 to 1600 mg.

26. The method of claim 23, wherein L-tyrosine is administered in a range of about 100 to 2000 mg.

27. The method of claim 23, wherein L-tyrosine is administered in a range of 350 to 1400 mg.

28. The method of claim 23, wherein N-acetyl cysteine is administered in a range of 100 to 2000 mg.

29. The method of claim 23, wherein N-acetyl cysteine is administered in a range of 250 to 1250 mg.

30. The method of claim 23, wherein alpha-lipoic acid is administered in a range of 50 to 1000 mg.
31. The method of claim 23, wherein alpha-lipoic acid is administered in a range of 150 to 600 mg.
32. The method of claim 23, wherein said administering is conducted on a continuous basis for at least 12 weeks.
33. The method of claim 23, wherein the neuropsychological impairment is associated with encephalopathy.
34. The method of claim 23, wherein the neuropsychological impairment is associated with traumatic brain injury.
35. The method of claim 23, wherein the neuropsychological impairment is associated with chronic fatigue.
36. The method of claim 23, wherein the CNS stimulant and nutrients are orally administered together in a combined tablet.
37. The method of claim 23, wherein the CNS stimulant is methylphenidate.
38. The method of claim 37, wherein the methylphenidate is administered in an amount of 2.5 to 40 mg/day.
39. The method of claim 38, wherein the methylphenidate is administered in an amount less than 20 mg/day.
40. The method of claim 23, wherein the CNS stimulant is modafinil.
41. The method of claim 37, wherein the modafinil is administered in an amount of 30 to 100 mg/day.

42. The method of claim 38, wherein the modafinil is administered in an amount of 30 to 50 mg/day.
43. The method of claim 23, wherein the CNS stimulant is armodafinil.
44. The method of claim 37, wherein the armodafinil is administered in an amount of 20 to 80 mg/day.
45. The method of claim 38, wherein the armodafinil is administered in an amount of 20 to 40 mg/day.
46. The method of claim 23, wherein the CNS stimulant is dexmethylphenidate.
47. The method of claim 37, wherein the dexmethylphenidate is administered in an amount of 2.5 to 10 mg/day.
48. The method of claim 38, wherein the dexmethylphenidate is administered in an amount of 2.5 to 5 mg/day.
49. The method of claim 23, wherein the CNS stimulant is an amphetamine.
50. The method of claim 37, wherein the amphetamine is administered in an amount of 2.5 to 20 mg/day.
51. The method of claim 38, wherein the amphetamine is administered in an amount of 2.5 to 10 mg/day.
52. The method of claim 23, wherein the CNS stimulant is atomoxetine.
53. The method of claim 37, wherein the atomoxetine is administered in an amount of 20 to 50 mg/day.
54. The method of claim 38, wherein the atomoxetine is administered in an amount of 20 to 25 mg/day.

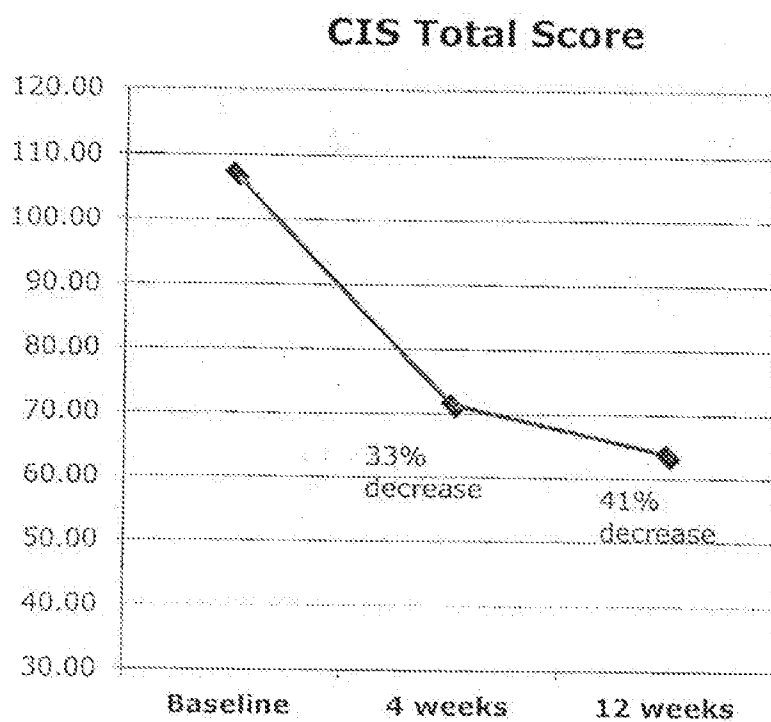


Figure 1

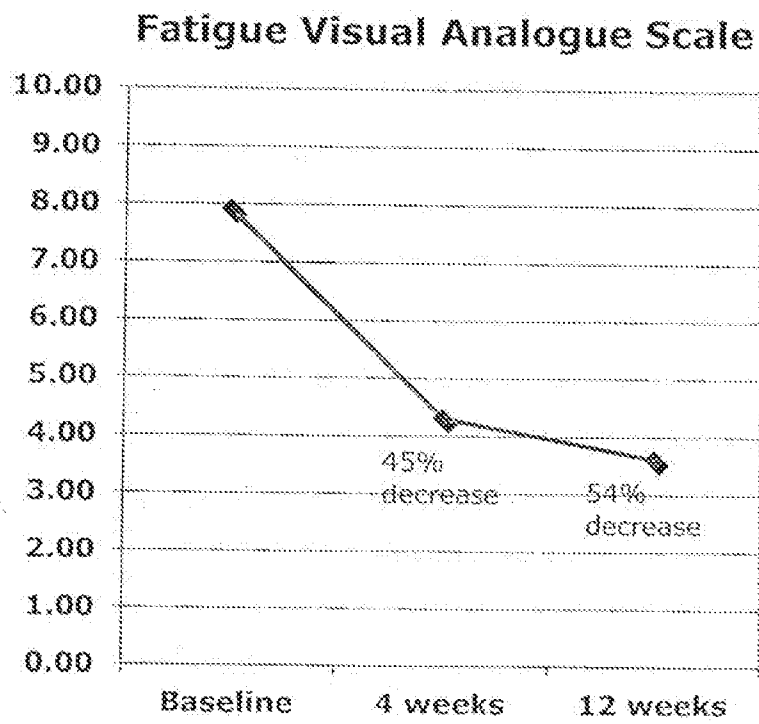


Figure 2

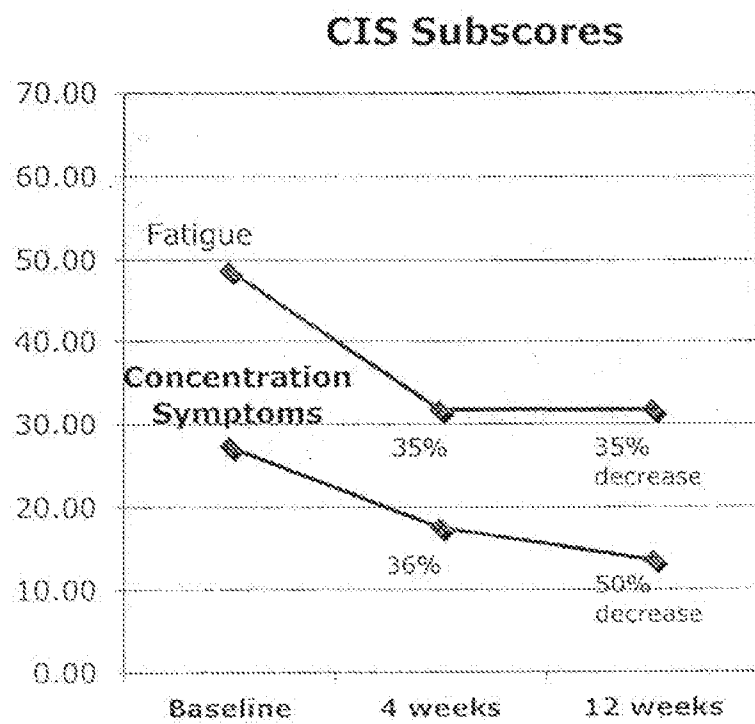


Figure 3

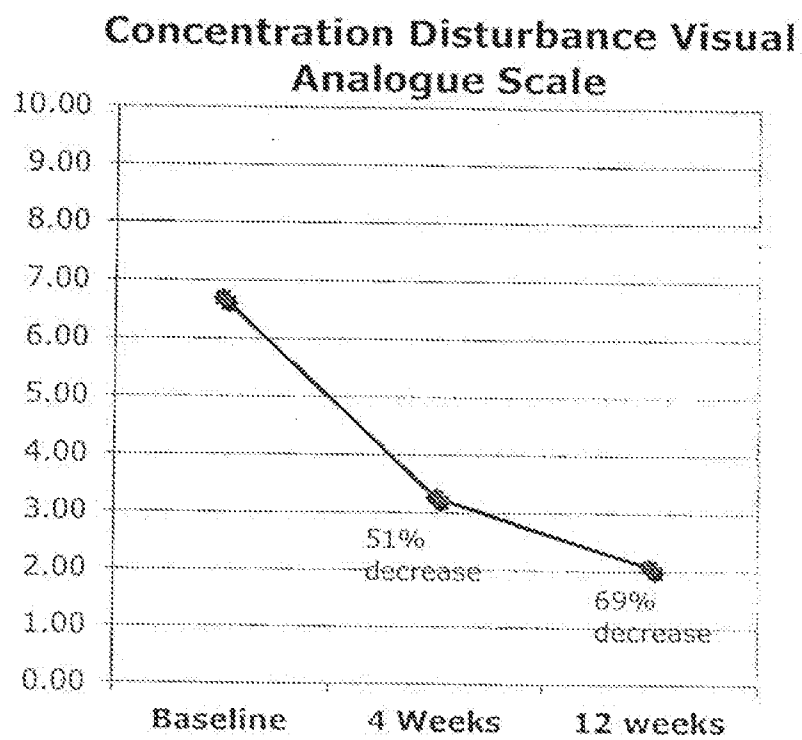


Figure 4