Metabolic Correction and Depression: Effect of a Supplement Combination

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Abstract

Depression is a mood disorder that causes changes in physical activity, appetite, sleep, and weight. The present study was aimed to investigate the effects of a combined supplement formula aimed to improve neurotransmitter metabolism in the treatment of this disorder. Five patients with depression were given combination dietary supplements with co-enzyme factored formula and were compared in pre- and post-treatment. Patients received daily supplementation consisting of a formulation of vitamins, minerals, herbs and fatty acids for six weeks. Severity of depression was measured using the Beck Depression Inventory-II (BDI-II) at baseline and was repeated at the sixth weeks post treatment. ANOVA with repeated measure was used to compare and track the changes during the study. The mean score of BDI decreased significantly (from 30 to 15) when patients were given the combination supplement formula at the end of week 6 ($p< 0.01$) compared to the baseline measures. The results of the present study suggest that the combination dietary supplement formula improves depressive disorder with no negative side effects and might be effective in the treatment of patients with depression.

Keywords: depressive disorder, dietary supplement, Puerto Rico

Resumen

La depresión es un trastorno del estado de ánimo que provoca cambios en el peso, apetito, sueño y actividad física. El presente estudio pretende investigar los efectos de una fórmula combinada de suplementos en el manejo de esta enfermedad con idea de mejorar el metabolismo de los neurotransmisores. Cinco pacientes con depresión recibieron suplementos dietéticos de combinación con co-enzimas y se compararon pre y post tratamiento. Los pacientes recibieron suplementación diaria de vitaminas, minerales, hierbas y ácidos grasos durante seis semanas. La gravedad de la depresión se midió usando el Inventario de Depresión de Beck-II en la visita inicial y se repitió en la sexta semana después del tratamiento. Se realizó una ANOVA con medidas repetida para comparar y realizar un seguimiento de los cambios ocurridos durante el estudio. La puntuación media del Inventario de Depresión de Beck disminuyó significativamente (de 30 a 15) cuando los pacientes recibieron la fórmula de suplementos al final de la sexta

semana sin efectos secundarios negativos ($p < 0.01$) en comparación con las medidas previas de línea de base, controlando para factores sociodemográficos (género, educación) y condiciones previas de salud. Los resultados del presente estudio sugieren que la suplementación pudiese ser de ayuda en el tratamiento de pacientes con depresión.

Palabras Clave: desorden depresivo, suplementación dietaria, Puerto Rico

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Major depression is one of the most common mental illnesses, affecting 6.7% (more than 16 million) of American adults each year (Substance Abuse and Mental Health Services Administration [SAMHSA], 2014). In 2030 it is expected to become the main cause of disability globally (Mensah & Collins, 2015). Although rates of depression are lower in blacks (24.6%) and Hispanics (19.6%) than in whites (34.7%), depression in blacks and Hispanics is likely to be more persistent (Budhwani et al., 2015).

Depressive disorders are nowadays a public health concern due to their high prevalence and poor results of the treatments currently available (Otte et al., 2016; Wang et al., 2017). Antidepressant medications alone or in combined therapy represent the main pharmacotherapeutic approach for the treatment of depression, with fluoxetine (FLU), paroxetine (PAR) and venlafaxine (VEN) among the most used antidepressant drugs worldwide (Khoo et al., 2015; Magalhaes et al., 2014; Pereira & Hiroaki-Sato, 2018). These drugs were designed to regulate brain serotonin levels by preventing the presynaptic resorption of synaptic serotonin (Mayo Clinic,

2018). This serotonin deficiency can be suffered in various degrees, leading to a host of mental, emotional, and behavioral problems, like depression.

Nevertheless, clinical outcomes achieved with antidepressant medications have been widely variable and overall unsatisfactory, suggesting that drug therapy optimization/individualization is required (Magalhaes et al., 2019). Therefore, traditional Chinese medicine, which reports significantly fewer side effects than modern medicine, is being researched as an alternative to modern antidepressants (Ri Kim et al., 2018). Natural herbs are attracting attention as therapeutic agents that can be administered over long periods with a reduced cost burden (Wang, Li & Huang, 2014). Like many other disorders, depression can be treated and relieved by lifestyles and nutritional changes.

Previous medical research report that about 10-30% of patients with depression do not respond to antidepressants (Saad Al-Harbi, 2012). Therefore, supplementation with micronutrients are increasingly of interest as an adjunct to Nutraceutical treatment or nutritional intervention (i.e., Metabolic Correction) has been recognized as effective by clinical professionals and consumers (Kleinman, 2004). Investigations suggest that several nutraceuticals and over-the-counter (OTC) drugs may be effective and safe as adjunct therapeutic agents to conventional available antidepressants (Dome et al., 2019). Nutraceutical might be defined as a substance that has physiological benefit or provides protection against chronic diseases (Nasri et al., 2014). Also, there are nutraceuticals that have a potential natural antidepressant (Targum & Mischoulon, 2009). In addition, this therapeutic modality has shown fewer side effects than conventional treatments (Fava & Davidson,1996). Metabolic Correction is a

functional biochemical/physiological concept that explains how improvements in cellular biochemistry help the body achieve metabolic or physiological balance (González & Miranda, 2016).

Studies on dietary factors and their relation to depression have shown that consumption of meals containing high amounts of carbohydrates cause insulin release. Insulin causes glucose entrance into the cells, and on the other hand make more amino acids such as tryptophan to cross the blood - brain barrier. This may increase neurotransmitter levels, especially serotonin, in the brain which can lead to improved mood (Solati et al., 2017). Amino acid tryptophan can be converted to serotonin in the body. Phenylethylamine (PEA) is metabolized from phenylalanine (Kapalka, 2010). It is a neurotransmitter and a hormone, and may act as neuromodulator for catecholamines (Kapalka, 2010). PEA increases extracellular levels of dopamine and modulates noradrenergic transmission (Kapalka, 2010). Thus, along with phenylalanine, supplementation with PEA has been presumed to have antidepressant effects. Dietary omega-3 fatty acids are provided from some especial plant and animal sources (especially some marine animals). Omega-3 fatty acids are involved in regulating corticotropin factor, stimulating the serotonergic pathway, preventing neuronal apoptosis, improving blood flow to the brain and regulating gene expression (Freeman et al., 2006). Folate and vitamin B12 insufficiencies have been associated with increased risk of depression (Almeida et al., 2015). Low folate status has been linked to depression and poor response to antidepressants (National Institutes of Health [NIMH], 2019). This might be related to folate's role in methylation reactions in the brain, neurotransmitter synthesis, and homocysteine metabolism (Huang et al., 2018; Gougeon et al., 2016). Low vitamin B12 serum levels have been associated with depressive symptoms (Petridou et al., 2016). Plausible biological mechanisms for the potential association between B-complex vitamins and depression have been demonstrated focusing on their role in the methionine synthesis (Petridou et al., 2016). The basis of this link may be that the synthesis of methionine requires a supply of both methyl groups from methyl-folate and also B12 vitamin as co-factor (Petridou et al., 2016). Methionine is in turn a precursor of S-adenosylmethionine, the main methyl donor in many methylation reactions in the brain including: (1) one-carbon metabolism, which is directly relevant to the production of key monoamine neurotransmitters in the brain: dopamine, serotonine, norepinephrine; (2) energy production and consumption by the brain tissue (thiamine); and (3) red blood cell formation and DNA synthesis (Petridou et al., 2016).

Serotonin, the precursor to melatonin, functions as an inhibitory neurotransmitter to reduce excitatory activity. Over time it can dampen the effects of dopamine and noradrenaline that stimulate over arousal, fear, anger, tension, aggression, violence, anxiety, and sleep disturbances. Serotonin plays an integral role in supporting feelings of wellbeing, calmness, security, relaxation, confidence, and concentration. Conversely, a deficiency of serotonin may be central in the development of depression, sleep disorders, obesity, and addictions.

The present study was designed to examine the effects of the *Private Label Combination Supplement Revive* in patients with depression. The combination in this formula included 5-hydroxytryptophan, Omega-3 fatty acids, B-complex vitamin, St. John's Wort, and Ginkgo Biloba.

Method

Participants and Procedure

The sample comprised five depressive adult patients, who were compared in pre- and post-treatment, with a first diagnoses of clinical depression. Those patients were referred to a Private Clinic in Ponce, Puerto Rico. Sampling started after obtaining consent approval from the patients and upholding ethical research protections for such patients, according to clinic protocols.

The patients were aged 18-55 years, three males and two females all with undergraduate studies.

The inclusion criteria included diagnosis of depressive disorder by a psychiatrist based on DSM-5, obtaining informed consent from the patients, no supplements usage at least four weeks before the study, not taking any medication except for those associated with depression status. In other words, all patients were taking antidepressants medications, Selective Serotonin Reuptake Inhibitors (SSRI). The exclusion criteria included pregnancy or lactation, severe psychotic symptoms, changing drug class, symptoms requiring hospitalization including suicidal thoughts and actions. Clinical research ethical principles were followed as for appropriateness and security of research subjects.

Intervention

Patients received the combination supplement consisting of vitamins, minerals, herbs, and fatty acids to be taken daily. The components of this combination supplement formula included: **5-hydroxytryptophan** (5-HTP) which is an intermediate metabolite of the amino acid L-tryptophan in the

biosynthesis of serotonin. Intestinal absorption of 5-HTP does not require the presence of other amino acids for biodegradation; therefore, it may be taken with meals without reducing its effectiveness. Unlike L-tryptophan, 5-HTP cannot be shunted into niacin of protein production. Therapeutic use of 5-HTP bypasses the conversion of L-tryptophan into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. 5-HTP is well absorbed from an oral dose, with about 70% ending up in the bloodstream. It easily crosses the blood-brain barrier and effectively increases central nervous system (CNS) synthesis of serotonin (Van Praag & Kahn, 1998). More information can be obtained in multiple articles that describe the importance of this type of supplementation (Asberg et al., 1976; Kahan & Westernberg, 1985; Martínez & González, 2017; Persson & Roos, 1967; Sano, 1972; Van Praag & Korf, 1970; Yaryura-Tobias & Bhagavan, 1977). **Omega-3 fatty acids:** The fluidity of the CNS (brain and spinal nerves) is directly linked to behavior, mood, and mental functioning. Diminished brain function can cause, or significantly worsen, depression (Ellis & Sanders, 1977). **B-complex vitamins** deficiency of B-vitamins can cause many nervous disorders including depression; thus, it is wisely to supplement with B-Complex for depression improvement (Bell et al., 1991). **St. John's Wort** (hypericum perforatum, 3% hyperacin), this herb/flower is indicated for mild to moderate depression and is best known for its Monoamino Oxidase (MAO) inhibitory activity. Monoamine oxidase is an enzyme that degrades serotonin, so by inhibiting the effect of MAO will prolong the halftime of serotonin (Harrer & Sommer, 1994). **Ginkgo Biloba:** 24% ginkgo flavone and flavone glycosides. This tree has been helpful when depression is linked to a decline in mental function, especially in the elderly. Ginkgo

works primarily by improving blood flow to the brain (Kleijen & Knipschild,1992).

Instruments

The Beck Depression Inventory-II, a valid questionnaire for screening depression for Puerto Rico (Rodríguez et al., 2006), physical activity questionnaire, three-day dietary recall, and anthropometric indices were completed in the beginning (6 weeks period) and end (12 weeks final period) of the study. Nutritionist IV software was used to analyze a three-day dietary recall (Yaryura-Tobias & Bhagavan, 1977). Macro and micronutrients intake were derived from the three-day dietary recall and compared between the two groups: experimental and control groups.

Also, at the beginning of the research (6 weeks period) and end of the study, (12 weeks final period) a blood sample of approximately 5 ml was taken after a 12-hour fasting state for general laboratory tests such as Complete Metabolic Panel (CMP), Urinalysis (U/A), Count Blood Cells (CBC) and T-3, T-4 & TSH (Thyroid hormone tests) and some nutrients/vitamins were evaluated (i.e., B vitamin complex and folic acid) and homocysteine.

Statistical Analysis

Data analysis was performed using SPSS version 16. Kolmogorov-Smirnov and chi-square tests were used to determine the normal distribution of quantitative data and to compare qualitative variables between the two times (pre and post), respectively. In the case of quantitative variables with normal distribution for comparison between the beginning and end of the intervention within the subjects, paired t-test, and for comparison between the two times, at the beginning or end of the intervention, t-test were used. The Wilcoxon and Mann-Whitney tests were used in the case of quantitative variables with non-normal distribution. To compare and track the change of means of quantitative variables that were measured three times (i.e., pre, post and a follow up) during the study period; analysis of variance (ANOVA) with repeated measure was done. Covariance analysis was performed to adjust for quantitative confounding factors.

Results

In this study, all 5 patients receiving the supplement formula showed clinical improvement as evaluated by the clinician. The patients were alike with respect to income, nonsmokers, and no other significant difference was observed between them. Furthermore, the patients were statistically similar in terms physical activity, weight, and Body Mass Index (BMI) during the study. No significant difference was observed regarding dietary intake of energy, carbohydrate, protein, cholesterol, and fiber. During the study, dietary intakes of micronutrients such as zinc, magnesium, iron, vitamins B1, B2, B3, B6, B12, and folic acid were not significantly different.

Depression scores as reported by the BDI-II decreased significantly as subjects are supplemented at the sixth week *(p* < 0.01), to the twelfth week of the study *(p* < 0.001) compared to the baseline (before the 6 weeks period).

At the end of the study (6 weeks), Beck scores were significantly lower (*p* < 0.05, from 30 to 15). Even after adjusting for the effect of dietary confounding factors, including intake of total fat, saturated fatty acids, Monounsaturated fatty acids (MUFA) and Polyunsaturated fatty acids (PUFA) fatty acids and magnesium. This difference still remained significant in the last follow up period of the research (twelfth week). Also, homocysteine and cholesterol values decreased significantly (*p* <0.05).

Discussion

The present study examined the effects of the *Private Label Revive* supplementation in patients with depression. The results of this study reveal that the combined supplementation formula might be effective in the treatment of patients with depression. Several of the findings show a metabolic role of each of the components of the formulation that was explained previously. The positive outcome suggests a synergistic activity of these components due to form and dose.

There is a recognition and extensive documentation that many depressed patients do not achieve full remission of symptoms or recover full daily functions, no matter they are in standard clinical treatment for depression. Consequently, augmentation strategies, like supplementation, that add additional medications to SSRIs treatments abound in clinical research and practice.

Amino acid tryptophan can be converted to serotonin in the body. Tyrosine amino acid can be synthesized from the amino acid phenylalanine and may enter into the biochemical pathways of dopamine and norepinephrine (Kravitz et al., 1984). Dietary omega-3 fatty acids are provided from some especial plant and animal sources (especially some marine animals). Omega-3 fatty acids are involved in regulating corticotropin factor, stimulating the serotonergic pathway, preventing neuronal apoptosis, improving blood flow to the brain and regulating gene expression (Freeman et al., 2006). Folate and B12 deficiency are associated with depression. About 10 to 30% of depressed patients have low serum folate levels and their response to antidepressants is weak. Early vitamin B12 deficiency leads to depression. This is due to the reduced synthesis of S-Adenosyl Methionine (Fava et al.,

1997). S-Adenosyl Methionine is associated with mood. The low concentrations in cerebrospinal fluid of depressed patients have been observed and it was found that increasing its plasma concentrations have improved the depressive symptoms (Bell et al., 1994). Also, of interest is the decrease of homocysteine and cholesterol measures which are consider risk factors to several diseases. In the present study, the supplementation formula significantly decreased the Beck depression scores.

We have to acknowledge that this report had a number of limitations. First, the results are based on a limited number of patients. Second, all five patients were taking antidepressants during the treatment protocol. It is possible that the benefits demonstrated by the patients could be mainly produced by the SSRI. Third, the results of this study only suggest that the supplementation could be effective in combination with the SSRI. The present study did not use a treatment group of depressive patients where they were treated solely by the combined supplements. Third, although all the patients were on a combination treatment, a score of 15 on the Beck Depression Inventory-II is indicative of a significant number of depressive symptoms. Maybe a more extensive period of treatment is necessary to obtain lower scores. Therefore, we suggest a more comprehensive study should be performed in a larger group of patients in a double-blind placebo-controlled form or waiting list control group.

Nonetheless, these results add to a growing body of literature implicating supplement formula are more benign and present limited toxicity than conventional antidepressants like fluoxetine or escitalopram. We recommend controlled studies that use wide-ranging doses and/or treatment delivery systems and compare their efficacy against the newer antidepressants. An article review suggests natural antidepressants (Rhodiola

rosea, chromium, 5-Hydroxytryptophan, and inositol) obtain promising results when combined with antidepressants (Lovieno, et al., 2011). A recent systematic literature search found more than 20 agents (e.g., S-Adenosyl-L-Methionine; folate; 3 fatty acids; curcumin; N-acetylcysteine; saffron; 5-hydroxytrpytophan; NSAIDS) that are supposedly effective in the augmentation of standard available antidepressants treatment (Dome et al., 2019). Our preliminary study suggests some nutraceuticals seem to have mood-improvement properties.

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