

Using nutraceuticals in the management of major depressive disorder (MDD)

Approach to be considered for sustainable healthcare systems

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Abstract

Purpose – The purpose of this paper is to study evidence-based records on the impact of some effective nutraceuticals on major depression disorder management; and describe the antidepressant properties of nutraceuticals to achieve health policy targets and maintain a sustainable healthcare system.

Design/methodology/approach – The literature was searched using MEDLINE (PubMed), Google Scholar, PsycINFO and Quertile databases and retrieving relevant published articles in peer-reviewed journals.

Findings – The results provided evidence of a range of nutraceuticals with potential benefits in the management of depression. Studies support the anti-depressant properties of S-adenosyl methionine, folinic acid, 5-hydroxytryptophan and omega-3 fatty acids. The results might represent evidence for an innovative adjunctive neurobiological line for the management and treatment of depression.

Practical implications – Randomized-controlled trials and evaluations continue to provide evidence for the use of nutraceuticals in the treatment of depression.

Social implications – Nutraceuticals emphasize the personalized medicine, which offers a psychophysical balance to the individual.

Originality/value – Nutraceuticals have specific antidepressant properties that may be beneficial in psychiatric populations and reduce pharmacotherapeutic side effects.

Keywords 5-hydroxytryptophan (5-HTP), Complementary and alternative medicine (CAM), Major depressive disorder, Nutraceuticals, Omega-3, S-adenosyl methionine (SAME)

Paper type General review

An overview of the problem

European public health is facing considerable challenges because of different social, political, environmental and lifestyle factors. Depression represents a major challenge for public health, affecting economic activity, social life, learning and the value of life beyond those of most physical diseases, and in particular, reported cases can lead to suicide attempts or suicide. According to the first report from the European Outcome of Depression International Network (ODIN) study carried out by Ayuso-Mateos *et al.* (2001), depressive disorder is a highly prevalent condition in Europe as it is reported to be 8.5 percent, for female and male the prevalence of depressive disorder is a highly prevalent condition in Europe as it is reported to be 8.5 percent for female and male with great occurrence (urban UK and urban Ireland), little occurrence (urban Spain) and average occurrence (the remaining places). According to a study carried out by Curran *et al.* (2007) on mental health and employment, depression was found to be the main reason for absence from work and premature retirement in many European countries. In addition, Sobocki *et al.* (2006) reported that depression is considered the most cost effective brain disorder in the region to manage,



accounting for 33 percent of the total cost. The World Health Organization (2013) reported that among the 20 countries with the highest percentages of suicides in the world, six are in the European region and annually, about one out of 15 people has depression in the WHO European region and four out of 15 have anxiety and other forms of depression (Figure 1).

Despite the advancement in psychopharmacologicals during the past few years and the better effects of using psychopharmacologicals than several years ago, management of major depression controlling is still a challenge that mental health workers face. Patients who are not satisfied with conventional treatment seek other treatments, especially complementary and alternative medicine (CAM), either in combination with conventional treatment or alone. According to Herman *et al.* (2012), CAM is cost-effective, safe and well tolerated by patients with mental and physical conditions.

Major depression disorder (MDD)

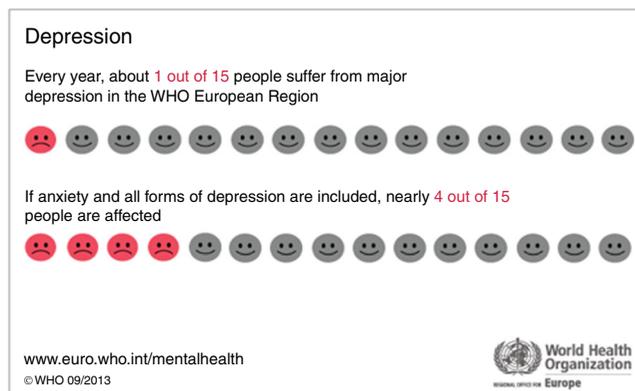
This is a psychological condition described by a general and determined low mood that is accompanied by loss of pleasure or interest in activities normally loved by a person and loss of self-esteem (Salmans, 1997).

The pathophysiology of MDD

The main physiological changes that occur in MDD are neuroendocrinological alterations, decrease in brain-derived neurotrophic factor, cytokine changes and monoamine impairment (Belmaker and Agam, 2008). There is a possibility to use a more broad therapeutic biological method to treat depression with an array of main neurobiological pathways by specific nutraceuticals (omega-3 fatty acids, S-adenosyl methionine (SAME), folic acid and 5-hydroxytryptophan (5-HTP)).

Nutraceuticals

According to Kalra (2003), nutraceuticals are substances arising from food with health benefits as well as essential nutritional value. It combines two words “nutrient” (a nutritious food constituent) plus “pharmaceutical” (a medical remedy), which were combined in 1989 by the Creator and Chairman of the Foundation of Innovation Medicine, Stephen L. DeFelice. Nutraceuticals include herbal products, dietary supplements, isolated nutrients and specific diets and processed foods such as soups, beverages and cereals, which supposedly offer health or medicinal benefits, and may aid the treatment and prevention of diseases. The role of nutraceuticals in human nutrition is one of the most significant areas of study, with wide implications for healthcare providers, consumers, food distributors and producers.



Source: www.euro.who.int/mentalhealth

Figure 1.
Depression in the
WHO European
Region

SAMe

SAMe is a molecule found in body fluids and tissues. It is composed of adenosine triphosphate and L-methionine (Bottiglieri *et al.*, 1988). SAMe was initially discovered in Italy by Cantoni (1952). It was found to be an effective cofactor in biological methylation reactions by Cantoni as a to give methyl groups to a variety of molecules in the body (Kresge *et al.*, 2005). Moreover, it is converted into homocysteine and adenosine (Baldessarini, 1987) (Figure 2). It is involved in several cellular functions including the metabolism and synthesis of neurotransmitters (Gören *et al.*, 2004). SAMe might also improve symptoms of depression through augmented serotonin turnover, decreased prolactin secretion, re-uptake inhibition of norepinephrine, enhanced dopaminergic action and increased phosphatidylcholine conversion (Papakostas, 2009). Although SAMe has been sold in particular European countries for many years for depression and other medical conditions (Shippy *et al.*, 2004) it is not approved legally for the treatment of depression in the UK.

L-folinic acid (the active form of folate)

Some studies in the literature propose that depression is related to folate deficiency (Coppen and Bolander-Gouaille, 2005). In addition, patients who have folate deficiency either show a slight improvement, a more severe depressive incident or greater probabilities of relapse when taking antidepressants (Fava *et al.*, 1997). Coppen and Bailey (2000) conducted a randomized, placebo-controlled trial to study the augmentation of the fluoxetine antidepressant action by folic acid. In total, 127 patients were randomly assigned to take either 500-microgram folic acid or a similar-looking placebo plus 20 mg fluoxetine daily. There was a significantly better improvement in the depression symptoms score in the fluoxetine plus folic acid group. A good response (> 50 percent reduction in score) was observed among 93.9 percent of women who received the folic acid supplement, whereas only 61.1 percent of women who received the placebo supplement showed improvement ($p < 0.005$).

Folate was found to be involved in the formation and metabolism of various monoamines, especially in the formation of SAMe from homocysteine (Fava and Mischoulon, 2009).

5-HTP

5-HTP, which results from L-tryptophan, is an important monoamine precursor that is needed for the formation of serotonin (Byerley *et al.*, 1987). A review of the literature was carried out by Shaw *et al.* (2002) to investigate the effect of 5-HTP or L-tryptophan in addition

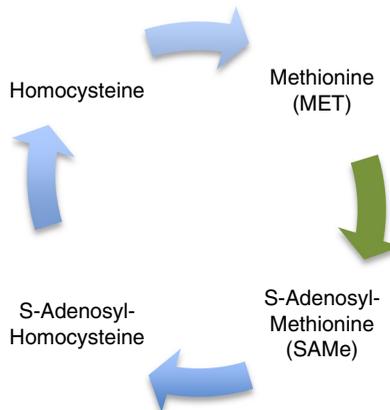


Figure 2.
Conversion of methionine into Homocysteine (Methyl transfer reaction)

Source: Khalifa (2016, unpublished work)

to antidepressants. Trials were searched in computerized general (PsychLIT, Medline and Embase) and specialized databases (Cochrane Collaboration Depression Cochrane Controlled Clinical Trials Register, Anxiety and Neurosis Controlled Trial Register). Trials included patients with unipolar depression or dysthymia, compared preparations of 5-HTP or tryptophan with placebo and included clinical outcomes assessed by scales assessing depressive symptoms. The results showed that 5-HTP or L-tryptophan, along with antidepressants, led to improved outcomes in boosting the antidepressant response.

According to Osiecki (2006), the co-factors magnesium, calcium, B6, folic acid and iron are essential in the metabolism and conversion of tryptophan into 5-HTP and B6, zinc, magnesium and vitamin to convert 5-HTP into serotonin (Figure 3).

Omega-3 fatty acids

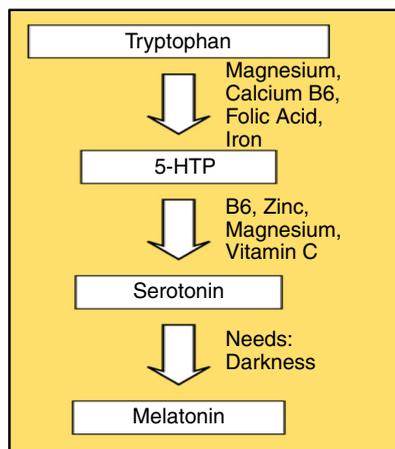
Recently, new beneficial effects of omega-3 poly unsaturated fatty acids (PUFA) were suggested, for example management for specific types of mental illness, such as depressive disorders (Grosso *et al.*, 2014). Depression might share some pathophysiological mechanisms with cardiovascular disease, specifically endothelial dysfunction, increased manufacture of pro-inflammatory cytokines and increased levels of plasma homocysteine (Severus *et al.*, 2001). The factors which affect omega-3 PUFA positive influence on depression might depend on their physiological content in the nervous system and their contribution toward neuroplasticity in addition to neurogenesis (Bourre, 2004). In addition, the anti-inflammatory ability of omega-3 PUFA might reduce the occurrence of inflammatory procedures in depression (Maes *et al.*, 2009).

The antidepressant action of omega-3 fatty acids occurs through the modulation of dopamine, norepinephrine and serotonin re-uptake, synthesis, degradation and receptor binding, resulting in the improvement of cell membrane fluidity and anti-inflammatory effects (Sarris *et al.*, 2012). A study carried out by Martins (2009) found that eicosapentaenoic acid (EPA) preparations, or those with higher EPA to docosahexaenoic acid (DHA) ratios, possibly have a greater antidepressant effect than DHA only.

Methodology

Search of the literature

Aimed search. The literature was searched through library databases (MEDLINE (PubMed), Google Scholar, CINAHL, PsycINFO, Cochrane Library databases and Quartile databases).



Source: Meyers (2000)

Figure 3.
Formation of 5-HTP
and serotonin
from tryptophan

Both conceptual and empirically published literatures on the uses of nutraceuticals in the management of depression were summarized. A review of the literature was performed to determine the mechanisms of action of these nutraceuticals.

Search strategy. The keywords and phrases used in the search were CAM, nutraceuticals, depression, antidepressant, SAME, folic acid, 5-HTP omega-3; sustainability and Europe. The reference lists from published studies and reports were searched for additional sources. Several electronic journals specializing in alternative medicine were searched. The overall search method yielded discussion papers and information from consultation papers, which were examined to abstract evidence, related to the present literature review objectives.

Selecting the articles and review resources

Inclusion criteria. Articles including reviews, population, intervention of nutraceuticals in depression management and outcomes, were used in this study intervention of nutraceuticals in depression management and outcomes required.

Topics of interest. It were the use of Nutraceuticals in mental disorders.

Evaluating the evidence. The final selection of articles was performed by a comprehensive review of each article, which was assessed by two individuals to prevent errors and omissions.

Discussion

The high prevalence and expenses for treating and managing MDD among individual, families and community, represents a major challenge for public health in Europe prevalence and association with increased and expenses for the individual, families and community. MDD is the first reason for absence from work and premature retirement in many European countries, resulting in noticeable social and occupational impairment and reduced quality of life (Donohue and Pincus, 2007).

Sequenced treatment alternatives to relieve depression (STAR*D) have confirmed that in patients with depression, multiple treatment trials are often required as only a small proportion of patients with MDD show improvements through initial treatment with selective serotonin reuptake inhibitors (SSRIs) (Fava *et al.*, 2003).

The huge range of abnormalities found with MDD pathophysiology such as neuroendocrinological changes, cytokine alterations and monoamine impairment may be improved with the use of adjunctive nutraceuticals by correcting the neurobiological mechanisms responsible for the disorder. Nutraceuticals such as SAME, folic acid, 5-HTP and omega-3 fatty acids may serve as possible treatments for improving the responses of SSRIs in patients with clinical depression. The above-studied nutraceuticals have the potential to show significant benefits in improving depression in patients who are non-responsive to current antidepressants (Shaw *et al.*, 2002; Papakostas, 2009).

Although SAME seems more costly, considering its rapid antidepressant action and its side-effect profile, it may have a specific impact on the relations of treatment dosage and duration, inpatient and outpatient care, management of patients who discontinue therapy and having drug time off work.

L-methylfolate is very useful in depressed patients who have folate deficiency because of the administration of anticonvulsant mood stabilizers and patients whose genotype codes to an enzyme that results in ineffective L-methylfolate formation. L-methylfolate regulates the activity of different monoamine neurotransmitters through methylation. These complex mechanisms should be examined to determine the mechanisms by which natural products aid the treatment of depression (Coppen and Bailey, 2000).

5-HT has been shown to be more efficient than placebo for the treatment of depression, but the proof remains inadequate to be decisive and more and larger investigations are required to define whether 5-HTP is actually useful for the treatment of depression.

Omega-3 PUFA as a therapeutic agent was effective in MDD patients and also for depressive patients without an MDD diagnosis. Researchers found that Omega 3 PUFA had a significant positive effect on MDD patients or patients who have depressive symptoms.

Many nutraceuticals control several main pathways involved in the pathogenesis and neurobiological pathways of depression; however, clinical trials usually focus on modulating just one or two neurochemicals. Nutrients usually work together; therefore, the specific effects of nutrient components may not be obvious. However, all studies confirmed the antidepressant evidence behind each component of the nutraceuticals. One probable limitation of nutraceutical research is the use of isolated nutrients as opposed to multi-component formulas.

Conclusions, implications and recommendations

- Considering the scale of the economic and social consequences and the costs of MDD, the benefits are great toward decreasing the occurrence and influence of MDD and to promote the mental health of the population as a whole.
- According to Friedli and Parsonage (2007), improvements in mental health can lead to better physical health together with reduced possibility of stroke and heart disease and reductions in alcohol and tobacco consumption and reduced obesity.
- Due to the low incidences of complete recovery of patients treated with antidepressants as a first-line treatment, in addition to the side and unknown effects of long-term use of these antidepressants, it is essential that mental experts must be focus on multiple treatment trials, consequently more interventions are essential. One of the emerging means to improve the non or low response to antidepressants is the use of nutraceuticals.
- The positive antidepressant action of nutraceuticals may represent an effective treatment option to improve the effectiveness of antidepressants and this may support the study of nutraceutical formulations for other medical disorders.
- With respect to the general safety characteristics of nutraceuticals, they must be used in a good safety profiles and therapeutic doses. However, the mechanism of action, bioavailability and absorption of nutraceuticals are still unclear; therefore, further studies are warranted.
- In Europe, an optimal public health approach is in place for mental health and CAM separately (Figure 4). However, there is a lack of CAM for mental health; therefore, useful information and significant research on complementary and traditional medicine, especially nutraceuticals, in relation to mental health are essential for an effective response, comprehensive decisions and evidence-based policy-making to achieve the European health policy targets “Investing in Health” and maintain sustainable healthcare systems.
- Complementary and traditional medicine especially nutraceuticals and its relation to mental health can be included in mainstream policies such as the National Programme for Improving Mental Health and Wellbeing in Scotland, Adolescents en Souffrance Report – France, etc.
- World Mental Health Day, usually on October 10, was organized by the World Health Organization to promote understanding and awareness of mental health issues, with different themes each year. Making (using CAM in mental health) a theme on World Mental Health Day will result in an optimal public health approach in Europe on the basis of combined knowledge, capability and expertise.



Figure 4. Examples of mental health and complementary medicine (CAM) activity in Europe

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