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Herbal Remedies and Nutritional Supplements in the Treatment of Depression: A Review

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ABSTRACT:

Herbal remedies and nutritional supplements in the treatment of depression: a review

Objective: To evaluate herbal remedies and nutritional supplements in the treatment of depression.

Methods: A computer-based search of Pubmed, Medline, Embase, Cinahl, PsycINFO, AMED, and the Cochrane Database of Systematic Reviews was performed. Trials were included if they were potential human trials assessing herbal remedies and nutritional supplements in the treatment of depression and utilized validated instruments to assess participant eligibility and clinical endpoints. Selection criteria of the study was decided and taken into consideration.

Results: Trials were identified that met all eligibility requirements. Individual trials investigating Hypericum extract (St John's Wort), Folate, Polyunsaturated fatty acids, S-adenosyl-L-methionine, Inositol, Ginkgo biloba, Selenium, Ginseng, Chromium and Glutamine were located.

Discussion: Results of the trials are discussed to form the basis of a recommendation. No good quality evidence was identified on which to base a recommendation except for Hypericum used in mild to moderate depression with the potential risk of drug interactions.

Conclusion: A number of herbal remedies and nutritional supplements were reviewed in order to form the basis of a recommendation in the treatment of mild-to-moderate depression.

Key words: Depression, herbal therapy, food supplements, hypericum extract (St John's wort), folate, polyunsaturated fatty acids, s-adenosyl-L-methionine, inositol, ginkgo biloba, selenium, ginseng, chromium, glutamine

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BACKGROUND

Between 5-10% of the population experience depression at any time in any given year srequiring psychiatric or psychosocial intervention. The World Health Organization has reported that depression's financial burden globally ranked fourth in 2000, and will increase by 2020 to be the second most costly disease. This paper focuses on the systematic review of herbal remedies and nutritional supplements available for the management of depression.

INTRODUCTION

Depression is a global health problem. According to the World Health Organization, it affects about 121 million people worldwide, and those numbers are increasing. It is estimated to be the leading cause of mental disability worldwide and is predicted to be the 2nd leading cause of all health disability by 2020 (1). Although global estimates are not available, depression costs more than US$ 83 billion annually in medical treatment and lost work place productivity to the US economy, according to a published report (2).

Depression typically presents as lowered mood, difficulty in thinking, loss of interest, and physical complaints such as headache, disturbed sleep, loss of energy, and change in sex drive (3-4). The prevalence of major depression is reported to be 7.5 percent in Australia, 8 percent in Canada, and 5.4-8.9 percent in the United States (5-6).

While there are many potential precipitating factors, it is currently believed that depression is primarily the result of biochemical alterations in the brain (6). Pharmaceutical treatments, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs), cause alterations in brain chemistry through neurotransmitter amplification and regulation and have been shown to be effective in the treatment of depression (4). Yet, a number of adverse reactions occur with pharmaceutical antidepressant administration, including anticholinergic effects, gastrointestinal effects including nausea and constipation, orthostatic hypotension, arrhythmias, weight gain, and sexual dysfunction (4).

In an attempt to avoid such unwanted adverse reactions, as well as being prompted by a desire to use something natural, individuals are seeking alternatives to pharmaceutical medications. Population-based studies carried out world wide have shown that the interest in herbal medicines and nutritional supplements continues to grow as an increasing number of people look at ways to improve their own lives and by using a variety of alternatives to conventional medicines (7-8). The use of these complementary and alternative (CAM) medicines is more common among patients with anxiety and severe depression according to a published study. This large-scale study found depression, anxiety and insomnia to be among the most common reasons for people to use complementary medicines. For example, 53.6% of respondents suffering from severe depression reported using complementary and alternative medicine for treatment during the 12 months before the survey (9). In the UK, estimates of the proportion of the general population using CAM range from 14% to 30% (10) and consumer surveys in other European countries indicate positive public attitudes toward the use of complementary therapies as one of the most popular forms of treatment (11). The findings of a large postal survey conducted in Australia (12) showed that people who were experiencing mild to moderate depression chose self-help strategies and complementary therapies such as St John's wort, meditation and nutritional supplements rather than seeking professional help. Because of wide spread use of these unconventional medicines, this systematic review was undertaken to evaluate clinical trials investigating the efficacy of herbal medicines, in the treatment of depression. It also provides an evidence based assessment of these medicines for depression in the adult population.

METHODS

Data Sources/Search Methods

A systematic review of the literature was carried out using an unambiguous search strategy. Databases searched include Pubmed, Medline, Embase, Cinahl, PsycINFO, AMED, and the Cochrane Library. Previous systematic reviews, meta-analyses and randomised controlled trials (RCTs) were hand searched for additional references with the search extended to identify observational studies where appropriate. The year range covered was 1998-2011 with variations depending on the topic. Internet searches were also carried out on various websites.

Review Methods

Trials were included in the review if they were prospective human trials assessing herbal remedies and nutritional supplements in the treatment of mild-to-moderate depression and utilized validated instruments to assess participant eligibility and clinical endpoints.

Inclusion and Exclusion Criteria

Selection criteria of the study was decided and taken into consideration. Treatments commonly available to patients without prescriptions were selected for inclusion. Studies were considered which included adults aged 18 years and over with no upper age limit. Exclusion criteria for studies was where there was no formal diagnosis by the International Classification of Disease (ICD) 9, ICD 10, Diagnostic Statistical Manual (DSM)-III or DSM-IV, or use of a recognized, validated and reliable measurement scale specifically for depressive symptoms. Further, studies in patient groups with clear indicators of severe depression or with significant psychological and/or physical comorbidities were also excluded.

RESULTS

Studies were identified that met all eligibility requirements for herbal remedies and nutritional supplements which have been reviewed for their efficacy in the treatment of depression. These were investigated to form the basis of a recommendation.

a) Hypericum Extract (St John's Wort)

Hypericum extract is a perennial herb of the genus Hypericum. Clinical trials have been conducted on specific Hypericum flower or leaf extracts. The composition of the extracts depends on both the raw material and the extraction methods used. Since there is no standard preparation or dose the amount of bioactive constituents can vary enormously (13-15). In one study a number of products on the German market contained only minor amounts of bioactive constituents (16). Although most clinical trials have been carried out using 300 mg preparations of Hypericum extract taken three times daily, doses rage from 600 mg to 1,800 mg daily (13).

A good quality Cochrane systematic review identified 29 studies with a total of 5,489 (range 30 to 388) patients; 18 involving comparisons with placebo and 17 with synthetic antidepressants. Only good quality trials involving patients with depression meeting criteria for the DSM-IV or ICD 10 were included. The severity of depression was described as mild to moderate in 19 trials and as moderate to severe in nine trials (one trial did not classify severity). Studies examined treatment with Hypericum extracts for four to 12 weeks (13). Results of placebo-controlled trials showed marked heterogeneity. In nine larger trials the combined response rate ratio (RR) was 1.28 (95% confidence interval (CI), 1.10 to 1.49) and from nine smaller trials was 1.87 (95% CI, 1.22 to 2.87). The cumulative evidence suggests that Hypericum extract has a modest effect over placebo in the treatment of mild to moderate depression in a similar range as standard antidepressants.

Results of trials comparing Hypericum extracts and standard antidepressants were statistically homogeneous with rate ratios (RR) of 1.01 (95% confidence interval (CI), 0.93 to 1.09) showing no difference in efficacy between treatments. In another, both in placebo-controlled trials and in comparisons with standard antidepressants, trials from German speaking countries (18 trials) reported findings more favourable to Hypericum than those conducted in other countries (11 trials). The reason for this is unclear. The evidence base for Hypericum for severe major depression is insufficient to draw conclusions (13). Further, no studies were identified comparing Hypericum extracts with psychological interventions.

Extracts of Hypericum may interact with other antidepressants, oral contraceptives and anticoagulants and may decrease the plasma level of a range of prescribed drugs such as anticoagulants, oral contraceptives, and antiviral agents (17-18). There is evidence that the combination of Hypericum extract with selective serotonin reuptake inhibitors can lead to serotonin overload or serotonin syndrome, particularly in older people (19). The number of drug interactions reported is increasing in the literature. In overdose there may be serious consequences in terms of confusion, autonomic instability, renal damage and muscle damage, particularly in combination with other psychotropic serotonergic drugs (20). Healthcare professionals should not advise use of extracts of Hypericum (St John's wort) for patients with depression due to the lack of standardization of dose and the risk of interactions with several common medications including the contraceptive pill. Where individual patients are using extracts of Hypericum (St John's wort) for treatment of depression, the general practitioner should facilitate full consideration of potential drug interactions.

b) Folate

Folate is required for the synthesis of dopamine, norepinephrine, and serotonin (21). It is also a key component of the methylation cycle, and deficiency of 1 or more components of this cycle leads to accumulation of homocysteine, which is associated with dementia, Parkinson disease, and cerebrovascular disease. People with folate deficiency are more likely to suffer from depression (22), are more likely to have more severe and longer lasting relapses (23), and are 6 times less likely to respond to antidepressant drugs (21). Folate has been evaluated as adjunctive therapy in depression in 3 small randomized controlled trials (RCTs). The first involved 53 patients with major depression who were taking lithium. After participants took 0.2 mg/d of folic acid or placebo for 1 year, no significant difference was found in Beck

Depression Scale scores between the folate and placebo groups (24). The second trial involved 24 patients with depression and folate deficiency (red blood cell folate level<200 µg/L). They were given 15 mg/d of L-methylfolate or placebo for 6 months in addition to their usual antidepressant medication. A small but significant improvement was noted (P<.05) (25). Finally, 127 depressed patients taking stable fluoxetine therapy were given 0.5 mg of folic acid daily for 10 weeks. Participants' Ham-D (Hamilton Rating Scale for Depression) scores declined by 2.6 (95% CI -0.13 to -5.07) points more in the folate group, a small but statistically significant change (P<0.05) (26). One study evaluated folate monotherapy, but it involved elderly patients with comorbid mild cognitive impairment (27).

There is insufficient evidence to recommend folate for the treatment of depression. Because folate deficiency is associated with poorer outcomes in depression, as well as mild cognitive impairment, megaloblastic anemia, and neural tube defects, it might be reasonable to screen and treat depressed patients for folate deficiency. It is important to note that folate supplementation at doses greater than 1 mg/d has been associated with increased risk of colorectal cancer. This issue is complicated by a new area of research: folate is methylated by methyltetrahydrofolate reductase (MTHFR) to produce methyltetrahydrofolate, the active form. Polymorphisms of the MTHFR gene increase the risk of depression (23) and cardiovascular disease. Genetic testing for MTHFR gene polymorphisms is now available; possessing these polymorphisms might increase the need for folate, vitamin B12, and other methylating agents. There is still insufficient evidence to guide clinical decisions in this important area of emerging research.

c) Polyunsaturated Fatty Acids (PUFAs)

Docosahexaenoic acid (DHA) and eicosapentenoic acid (EPA) are long-chain polyunsaturated fatty acids, the primary dietary source of which is oily seafood. Alpha-linolenic acid, an omega-3 precursor found in flax, soy, canola, and walnuts, is poorly converted in most humans and thus is not an important source of omega-3 fats (28). Neurons contain high levels of omega-3 fatty acids, where they influence phospholipid membrane fluidity, receptors, ion channels, and neuroendocrine regulation and inflammation (29). Depression is less prevalent in societies with high fish consumption, and depressed patients have significantly lower red blood cell omega-3 levels (P < .05) (30). It is believed that substantial losses occur during pregnancy to supply the fetal brain, and this might be linked to postpartum depression (30). Increasing consumption of inflammatory omega-6 fatty acids in the 20th century has made relative omega-3 deficiency more common (31).

A recently updated systematic review identified 35 RCTs involving 2949 patients. The trials used doses ranging from 0.5 to 9.6 g/d for 4 to 28 weeks. In the 16 RCTs that enrolled only patients diagnosed with major depressive disorder (MDD), the pooled standardized mean difference (SMD) was 0.41 (95% CI 0.26 to 0.55), which represents a 3- to 4-point change in Ham-D scores. Heterogeneity among the studies was analyzed and revealed publication bias, as well as greater effects in patients with more severe baseline depression. No benefit was seen in trials that enrolled patients without a diagnosis of MDD. No clear dose-response relationship was identified. There was no clear difference in terms of efficacy between EPA and DHA (32).

Omega-3 fatty acids show promise for the treatment of depression, but further research is needed to better understand sources of heterogeneity. It should be remembered that depression is not a specific disease; it is a syndrome that likely represents a number of different underlying pathophysiologic possibilities. Low levels of omega-3 fatty acids could represent one cause of depression. Diagnostic evaluation of red blood cell omega-3 levels should become increasingly available and might prove useful in this regard. If patients wish to supplement their diets with omega-3 fatty acid fish oil capsules, most clinicians recommend using a total dose (EPA and DHA combined) of at least 1 g/d. The most common side effect is experiencing a fishy taste. There is a theoretical increased risk of bleeding based on antiplatelet effects, but there is good evidence that this does not occur. Several large trials have failed to identify any increased risk of clinically significant bleeding with omega-3 use (33).

d) S-Adenosyl-L-Methionine (SAMe)

S-adenosylmethionine (SAM-e) is a naturally occurring molecule present in all human cells. Like folate and vitamin B12, SAM-e is involved in the methylation cycle;

it acts as a methyl donor to membrane phospholipids, myelin, choline, catecholamines, and other molecules important for brain function (34), affecting receptor function, membrane fluidity, and neurotransmitter production (35). Depressed patients have low levels of serum and cerebral spinal fluid SAM-e, and supplementation raises levels of SAM-e, dopamine, and other neurotransmitters in the brain (36-37). Italian researchers first noted its antidepressant effects in the 1970s (35).

There is some evidence supporting the benefit of SAM-e in treating depression. A recent systematic review reported benefit in 7 of 7 trials using parenteral SAM-e and in 4 of 5 studies using oral SAM-e at doses of 1600 mg/d (35). Of the 5 studies using oral SAM-e, it was equivalent to TCAs in 3. One study was large (n = 281) and reported a 12.5-point reduction in Ham-D scores in both groups after 6 weeks. Drug-related side effects occurred in 5% of SAM-e patients versus 20% of TCA patients (38). In the remaining 2 trials, it was superior to placebo in 1. The negative trial involved an unstable formulation of SAM-e that has since been withdrawn, as reported by the authors (39). There is some evidence to support the use of SAM-e, but this requires confirmation by larger studies. Side effects are uncommon, but occasionally nausea, gastrointestinal upset, and anxiety can occur.

e) Inositol

Inositol is an isomer of glucose and a naturally occurring compound which is widely available as a dietary supplement. All randomised controlled trials that compare treatment with inositol, whether as monotherapy or adjunctive therapy, to an alternative treatment, whether another antidepressant medication or placebo, for patients with a diagnosis of depressive disorder were considered. Four trials were identified, with a total of 141 participants. These were short term trials of double-blind design. The trials did not show clear evidence of a therapeutic benefit, or any evidence of poor acceptability. It is currently unclear whether or not inositol is of benefit in the treatment of depression. Ongoing studies should reduce this uncertainty (40).

f) Ginkgo biloba

Ginkgo biloba, also known as the Maidenhair tree, is a unique species of tree, the fruits and seeds of which are used in traditional Chinese medicine. Leaf extracts are available as supplements. No good quality evidence was identified for the use of Ginkgo biloba as stand-alone treatments for patients with depression.

g) Selenium

Selenium is a non-metallic element which rarely occurs in its elemental state in nature. No good quality evidence was identified for the use of selenium as stand-alone treatments for patients with depression.

h) Ginseng

Ginseng is a perennial plant which grows in eastern Asia. The root extract is widely available as an herbal remedy. No good quality evidence was identified for the use of ginseng as stand-alone treatments for patients with depression.

i) Chromium

Chromium is a mineral that humans require in trace amounts. No good quality evidence was identified for the use of chromium as stand-alone treatments for patients with depression.

j) Glutamine

Glutamine is a naturally occurring, non-essential amino acid. No good quality evidence was identified for the use of glutamine as stand-alone treatments for patients with depression.

CONCLUSION

No applicable evidence was identified on which to base a recommendation except for Hypericum used in mild to moderate depression with the potential risk of drug interactions. Physicians should consider screening for and treating folate deficiency, but the benefits of folate supplementation remain unclear. Limited evidence supports the use of omega-3 fatty acids and SAM-e, but further studies are required with sound methodologies for individual herbal remedies and nutritional supplements to form the basis of a recommendation.

References:

1. World Health Organization. WHO traditional medicines strategy 2002-2005. Geneva, Switzerland: World Health Organization; 2002.

2. Dhingra S, Parle M. Non-drug strategies in the management of depression: A comprehensive study of systematic review and meta-analysis of randomised controlled trials. J Neurosci Behav Health 2011; 3(5):66-73.

3. Tierney LM, McPhee SJ, Papadakis MA, eds. Current Medical Diagnosis & Treatment. 45th ed. San Francisco, CA: McGraw-Hill; 2006:1065-66.

4. Mann JJ. The medical management of depression. N Engl J Med 2005; 353:1819-34.

5. Smith AJ, Sketris I, Cooke C, Gardner D, Kisely S, Tett SE.A comparison of antidepressant use in Nova Scotia, Canada and Australia. Pharmacoepidemiol Drug Saf 2008;17(7):697-706.

6. Andrews G, Titov N. Depression is very disabling. Lancet. 2007;370(9590):808-9.

7. Thomas K, Coleman P. Use of complementary or alternative medicine in a general population in Great Britain. Results from the National Omnibus survey. J Public Health (Oxf.) 2004; 26(2):152-7.

10. Zhou SF, Lai X. An update of clinical drug interactions with the herbal antidepressant St. John's wort. Curr Drug Metab 2008;9(5):394-409.

11. Kessler RC, Soukup J, Davis RB, Foster DF, Wilkey SA, Van Rompay MI, et al. The uses of complementary and alternative therapies to treat anxiety and depression in the United States. Am J Psychiatry 2001; 158(2):289-94.

12. Sharma U. Complementary medicine today: practitioners and patients. London, UK: Routledge; 1992.

13. Fisher P, Ward A. Complementary medicine in Europe. BMJ 1994;309(6947):107-11.

14. Jorm AF, Korten AE, Christensen H, Jacomb PA, Rodgers B, Parslow RA.Association of obesity with anxiety, depression and emotional well being: a community survey. Aust N Z J Public Health. 2003;27(4):434-40.

15. Linde K, Berner M, Kriston L. St John's wort for depression (Cochrane Review). In: The Cochrane Library, Issue 4, 2008. London:Wiley.

16. Pilkington K, Boshnakova A, Richardson J. St John's wort for depression: time for a different perspective? Complement Ther Med 2006; 14(4):268-81.

17. Fava M, Alpert J, Nierenberg AA, Mischoulon D, Otto MW, Zajecka J, et al. A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol 2005; 25(5):441-7.

18. Wurglics M, Lobbert SS, Dingermam T, Schubert-Zsilavecz M. Rational and traditional St. John's wort preparations: Consequences for treatment of depression. Dtsch Apoth Ztg 2003; 143(13):66-70.

19. Clement K, Covertson CR, Johnson MJ, Dearing K. St. John's wort and the treatment of mild to moderate depression: a systematic review. Holist Nurs Pract 2006; 20(4):197-203.

20. British National Formulary 61. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2011.

21. Ernst E.The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. Ann Intern Med. 2002;136(1):42-53.Baxter K (ed), Stockley's Drug Interactions 8. [CD-ROM] London: Pharmaceutical Press, 2008.

22. Farah A. The role of L-methylfolate in depressive disorders. CNS Spectr 2009; 14(1 Suppl 2):S2-S7.

23. Morris DW, Trivedi M, Rush AJ. Folate and unipolar depression. J. Altern. Complement Med 2008; 14(3):277-85.

24. Stahl SM. Novel therapeutics for depression: L-methylfolate as a trimonoamine modulator and antidepressant-augmenting agent. CNS Spectr 2007; 12(10):739-44.

25. Coppen A, Chaudhry S, Swade C. Folic acid enhances lithium prophylaxis. J Affect Disord 1986; 10(1):9-13.

26. Godfrey PS, Toone BK, Carney MW, Flynn TG, Bottiglieri T, Laundy M, et al. Enhancement of recovery from psychiatric illness by methylfolate. Lancet 1990; 336(8712):392-5.

27. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. J Affect Disord 2000; 60(2):121-30.

28. Passeri M, Cucinotta D, Abate G, Senin U, Ventura A, Stramba Badiale M, et al. Oral 5'-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a doubleblind multicenter study. Aging (Milano) 1993; 5(1):63-71.

29. Freeman MP. Omega-3 fatty acids in major depressive disorder. J Clin Psychiatry 2009; 70(Suppl 5):S7-S11.

30. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. J Clin Psychiatry 2007; 68(7):1056-61.

31. Freeman MP. Omega-3 fatty acids and perinatal depression: a review of the literature and recommendations for future research. Prostaglandins Leukot. Essent. Fatty Acids 2006; 75(4-5): 291-7.

32. Kris-Etherton PM, Harris WS, Appel LJ; Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Arterioscler Thromb Vasc Biol 2003;23(2):20-30.

33. Appleton KM, Hayward RC, Gunnell D, Peters TJ, Rogers PJ, Kessler D, Ness AR.Effects of n-3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. Am J Clin Nutr 2006;84(6):1308-16.

34. Harris WS. Expert opinion: omega-3 fatty acids and bleeding-cause for concern? Am. J. Cardiol. 2007; 99(6A):44-6.

35. Papakostas GI, Alpert JE, Fava M. S-adenosyl-methionine in depression: a comprehensive review of the literature. Curr Psychiatry Reports 2003; 5(6):460-6.

36. Papakostas GI. Evidence for S-adenosyl-L-methionine (SAM-e) for treatment of major depressive disorder. J Clin Psychiatry 2009; 70(Suppl 5):S18-S22.

37. Thomas CS, Bottiglieri T, Edeh J, Carney MW, Reynolds EH, Toone BK. The influence of S-adenosylmethionine (SAM) on prolactin in depressed patients. Int Clin Psychopharmacol 1987;2(2):97-102.

38. Bottiglieri T, Godfrey P, Flynn T, Carney MW, Toone BK, Reynolds EH. Cerebrospinal fluid S-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral S-adenosylmethionine. J Neurol Neurosurg Psychiatry 1990; 53(12):1096-8.

39. Delle Chiaie R, Pancheri P, Scapicchio P. Efficacy and tolerability or oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (SAMe) in the treatment of major depression: comparison with imipramine in 2 multicenter studies. Am J Clin Nutr 2002; 76(Suppl):1172S-S6.

40. Fava M, Rosenbaum JF, Birnbaum R, Kelly K, Otto MW, MacLaughlin R. The thyrotropin response to thyrotropin-releasing hormone as a predictor of response to treatment in depressed outpatients. Acta Psychiatr Scand 1992; 86(1):42-5.

41. Taylor MJ, Wilder H, Bhagwagar Z, Geddes J. Inositol for depressive disorders (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. London: Wiley.