CNI604 1/98
CLINICAL NUTRITION INSIGHTS

Vol. 6, No. 4

A Natural Approach to Depression

BY JOHANNE ROSE L.AC.

ABSTRACT: *Depression is a chronic and recurrent disorder that is associated with significant physical and social dysfunction; still, it remains under-diagnosed and under-treated in all age groups. It is a common clinical problem seen in primary care, with 70% of prescriptions for antidepressants now written by primary care physicians. The diagnosis of depressive disorders is made in the absence of other medical conditions that may precipitate a depression. However, the interrelationship between mental and general medical disorders should not be overlooked. Several neurotransmitters have been implicated in the etiology of major depression, most notably serotonin. In addition, psychosocial precipitants such as stressful life events may factor heavily in the onset of depression. A variety of nutritional factors, such as folic acid, inositol, and B vitamins, may play a role in the etiology of depression. A nutritional approach that encompasses these nutrients, as well as herbal therapies such as St. John's wort, may prove useful in the treatment of mild to moderate depression.*

Clinical depression, in its various forms, affects up to 14 million people in the U.S in any given year.[1,2] Epidemiological surveys suggest that women are more likely than men to develop major depression, and although the reason for this is not clear, it is most likely due to a combination of biological and psychosocial factors.[3,4] In addition to individual suffering, depression results in tens of thousands of deaths by suicide, an increase in morbidity and mortality from medical illnesses whose course is aggravated by an associated depression, a disruptive effect on family life, and an economic loss of billions of dollars.[2] Despite a high prevalence of depression in patients of all ages, it is under-diagnosed and under-treated by primary care and other non-psychiatric health care providers — the practitioners most likely to see the patient initially.[1,2,5]

RECOGNIZING DEPRESSION

The character, intensity, and duration of depression can vary from periodic bouts of "the blues" to persistent thoughts of suicide and can be classified as mild, moderate, or severe. The mildly depressed patient may appear on the surface to be a "low achiever" or have a lethargic personality, with deeper assessment revealing an underlying mood disturbance. The more common symptoms of mild to moderate depression include feelings of sadness and dejection, sleep disturbances, decreased energy, poor concentration, and significant weight loss or gain.[5,7,8] An individual may be diagnosed with a major depressive disorder if he has experienced one or more major depressive episodes (see Table 1).[5,8]

It is important to keep in mind that depression can be seen in any health care setting or type of practice. Consequently, it is necessary for all practitioners to be able to recognize and accurately diagnose depression, whether present alone or in patients with various somatic complaints or other conditions.[1] Differentiating depression and physical illness is often difficult and presents an especially significant challenge in the diagnosis and treatment of depression in the elderly.[1]

Table 1. DSM-IV Criteria for Major Depressive Episode[5,8]

At least 5 of the following symptoms must be present for at least a 2-week period, and must include #1 or #2 below:

1	Depressed mood on a consistent basis.
2	Markedly diminished interest or pleasure in all or nearly all activities.
3	Sleep disturbance (insomnia or hypersomnia).
4	Persistent feelings of guilt or worthlessness.
5	Decreased energy or fatigue.
6	Impaired concentration or indecisiveness.
7	Significant weight loss/gain.
8	Psychomotor agitation/retardation.
9	Recurrent thoughts of death or suicide.

Many patients with recurrent or chronic physical disorders experience depression that frequently aggravates the disability and sets up a vicious circle.[6] In addition, depression may be disguised in somatic form with what appear to be symptoms of organic disease, with the emotional disturbance often overlooked or even denied by the patient.[6] The patient history, physical examination, and laboratory results will be very important in establishing the proper diagnosis. Laboratory tests such as a thyroid profile, complete blood count, renal and liver function tests, and blood glucose may be necessary to rule out metabolic, endocrine, or infectious disorders as well as effects of drugs.[5,7]

Depressive illness is a major cause of suicide, and recognition and treatment of depression are the most important contributions a practitioner can make to suicide prevention.[6] Suicide causes 15% of deaths in untreated mood disorders and tends to occur within 4 to 5 years from the first clinical episode. The recovery phase from depression, when psychomotor activity is returning to normal but the mood is still dark, is a major risk period, as are the premenstrual phase and personally significant anniversaries (see Table 2).[6]

Table 2. High Suicide Risk Factors[6]

Personal and Social Factors	Clinical Features and Symptoms
• Age >55 years	• Depressive illness, especially at onset or toward end of illness
• Recent separation, divorce, or widowhood	• Marked motor agitation, restlessness, and anxiety
• Social isolation with real or imagined unsympathetic attitude of relatives or friends	• Marked feelings of guilt, inadequacy, and hopelessness; self-denigration or nihilistic delusion
• Impulsive, hostile personality	• Severe hypochondriacal preoccupations; delusional conviction of physical disease (e.g., cancer, heart disease, or sexually transmitted disease).
• Personally significant anniversaries	• Alcohol or drug abuse
• History of suicide or affective disorder in family	• Physical illness that is chronic, painful, or disabling
• Unemployment or financial difficulties	
• Previous suicide attempt	

ETIOLOGY OF DEPRESSION

Depression is an illness considered to be mediated by brain neurotransmitters and amenable to treatment that alters neurotransmitter regulation via their synthesis, reuptake, or degradation.[8] Norepinephrine and serotonin have been primarily implicated with a lesser role for dopamine.[8,9] The monoamine hypothesis of depression postulates a deficiency in serotonin and/or norepinephrine or an underlying abnormality in neurotransmitter receptor function.[3,10] Serotonin is believed to play a multifunctional role in depression because of its involvement in the regulation of mood, sleep, vigilance, memory and learning, feeding, and sexual behavior, all of which are deranged to varying extents in patients with severe depression.[10]

The synthesis of serotonin in the brain is dependent on the availability of its amino acid precursor tryptophan from plasma.[3] A recent double-blind, crossover study of 15 women assessed whether lowering of brain serotonin activity by depletion of tryptophan could provoke a short-term relapse of clinically significant symptoms in women vulnerable to major depressive disorder.[3] Seven hours after drinking a tryptophan-free amino acid mixture, 10 of the 15 women experienced temporary but clinically significant depressive symptoms. No changes in mood were seen after taking the nutritionally balanced amino acid mixture. Interestingly, other studies have shown that the degree of lowering of mood after tryptophan depletion is related to the susceptibility of the subject to depression, with a significantly greater effect seen in subjects with a family history of depression compared to normal subjects.[11]

While depression is biochemically mediated, psychosocial precipitants such as stressful life events may factor heavily in the onset of depression.[8] Symptoms of anxiety disorder frequently complicate depressive disorders.[7] Prolonged anxiety states will result in high cortisol levels, which have been associated with depression. An intimate relationship also exists between depression and illnesses such as cardiovascular disease, certain cancers, and disorders of the thyroid and adrenal glands.[5,6] The order of cause and effect is unclear; depression can be an early sign and a result of physical illness. The chronic pain and depression phenomenon is circular, and like other comorbid conditions, both must be treated.

A variety of nutritional factors, such as folic acid, inositol, and vitamins C, B_6, and B_{12}, are involved in the synthesis of neurotransmitters and therefore may be implicated in the pathogenesis of depression.[12,13] One researcher has even proposed a nutritional deficiency model for depression in which emotional strain may provoke overactivity of neurotransmitter production, leading to increased demand on their precursors (tyrosine, tryptophan, choline) and catalytic cofactors (vitamins B_6, B_{12}, C, and folate).[12] This situation might be conducive to a state of negative balance in these neurotransmitter functions, especially in a state of poor nutrition.

CONVENTIONAL TREATMENT OF DEPRESSION

Conventional treatment options for depression include numerous forms of psychotherapy, medication, or a combination of the two.[2,5,6] The three main antidepressant classes are monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs).[8,10,14] The main mechanisms by which these antidepressants have their effect are through inhibition of neurotransmitter degradation, reuptake blockage of the neurotransmitter, or blockage of the receptor site for the neurotransmitter.[8] While the older MAOIs and TCAs are effective antidepressants, they cause significant and, at times, dangerous side effects.[2,14] SSRIs, such as Prozac, offer a more tolerable side effect profile and their use has become widespread; however, important side effects such as nausea and vomiting, headache, insomnia, anxiety, and sexual dysfunction do occur.[2,8,15] SSRIs are frequently prescribed to patients who do not meet the criteria for a major depressive episode but rather have dysthymia or an unspecified dissatisfaction with life.[8]

While a patient who is severely depressed or suicidal should be treated with the appropriate medical intervention, those suffering from mild to moderate depression may benefit from nutritional and herbal supplementation. These therapies often have an equally powerful ability to produce the same chemical changes as antidepressant drugs. When combined with appropriate counseling and lifestyle changes, such as increased exercise and avoidance of caffeine, the use of natural remedies may provide relief to those who suffer from mild to moderate depression.

NUTRITIONAL AND HERBAL SUPPORT FOR DEPRESSION

• Folic Acid (folate) and Vitamin B_{12}

Folic acid and vitamin B_{12} are essential in several metabolic pathways in the central nervous system (CNS) and their metabolism is intimately related.[16] Both folate and vitamin B_{12} participate in the synthesis of norepinephrine, dopamine, and serotonin and also act as coenzymes in the methylation pathways that synthesize

S-adenosylmethionine (SAM).[11,12] SAM is the main methyl donor in the brain and has been shown to possess effective antidepressant properties.[11] Folic acid is required for the synthesis of SAM by donating its methyl group to homocysteine to form methionine (a reaction catalyzed by vitamin B_{12}), which is the immediate precursor of SAM.[16-19] In folic acid and vitamin B_{12} deficiency this reaction may become severely impaired resulting in reduced SAM synthesis and a considerable elevation in plasma homocysteine levels.[18] The neurotoxic effects of elevated homocysteine may also play a role in the neurologic and psychiatric disturbances that are associated with folate and B_{12} deficiency.[18,20]

In a study of 100 consecutive patient admissions with severe depression, low serum folate and vitamin B_{12} concentrations were found in 24% and 13% of the cases, respectively.[12] Low folate levels have been associated with mood disturbance, whereas low vitamin B_{12} has been more often associated with organic disorders and psychosis.[21] More than a dozen studies indicate that between one-third and one-half of psychiatric patients have a folate deficiency.[11,16] Folate levels have been shown to be significantly lower in patients with major depressive disorder than normal controls or other psychiatric patients.[19,22,23] Lower folate concentrations were associated with a greater severity of depression. In a recent study, folate levels were measured in 213 patients with major depressive disorder.[24] These patients were then treated with the antidepressant fluoxetine (Prozac) for 8 weeks to measure treatment outcome. The study showed that patients with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to fluoxetine treatment.

There is growing evidence that, irrespective of whether the deficiency is primary or secondary to the psychiatric disorder, folate supplementation may improve mental function.[16] In a double-blind, placebo-controlled trial of 24 patients with major depression and borderline or definite red blood cell folate deficiency (<200 µg/l), patients received 15 mg/day oral methylfolate or placebo for 6 months in addition to standard psychotropic treatment.[25] The methylfolate group showed significant improvement in clinical and social recovery scores compared to the placebo group. In an open study of 36 chronic alcoholics with major depression, patients were given 90 mg/day methylfolate for 4 weeks as an antidepressant.[17] Significant improvement of depressive signs and symptoms was reported with no adverse side effects.

While some studies have given patients up to 90 mg/day methylfolate without side effects, folate given in pharmacological doses (15 mg/day) to *healthy* volunteers was associated with toxic effects such as altered sleep patterns, malaise, irritability, and over-activity.[12] However, most studies of depressed patients have used 15 mg/day without side effects. One researcher suggests that, because a significant effect was obtained with a dose of 0.2 mg/day in one study, doses below 1 mg/day may be appropriate for folic acid supplementation, which is more than the usual daily dietary intake.[26] It appears that a dosage range of 0.2 mg to 15 mg of folic acid per day is appropriate.

• Inositol

Inositol is a simple sugar-like compound present in the normal diet that acts as a messenger within cells.[27] It is the precursor of the phosphatidylinositol (PI) second messenger system in the brain. The PI cycle is the second messenger system for numerous neuro-transmitters including serotonin. It is hypothesized that inositol may be deficient in some brain systems in depression; low inositol levels could cause second-messenger dysfunction and thereby depression.[27,28] In Europe, over-the-counter inositol has long been used as a folk remedy for anxiety and depression.[27] However, inositol passes the blood-brain barrier poorly and doses needed for clinical studies are high (6 g to 12 g/day).[28]

After an encouraging open trial of 6 g/day of inositol for treatment-resistant depression, researchers performed a double-blind controlled trial for 28 depressed patients (12 g/day for 4 weeks).[27] Significant overall benefit from treatment with inositol compared to placebo was found at week 4 but not week 2 on the Hamilton Depression Scale. A follow-up double-blind controlled trial of inositol treatment in panic disorders revealed significant benefit from the inositol (12 g/day for 4 weeks). No significant side effects were reported.

• St. John's Wort

St. John's wort *(Hypericum perforatum)* has been widely researched for its antidepressant effects and recent research has focused on its potential as an antiviral agent. It has a long history of use for a multitude of indications: vulnerary (wound healing), diuretic, depression, neuralgic disorders, anti-inflammatory, and as a sedative.[29,30] St. John's wort has become increasingly popular in Germany, where in 1994, 66 million daily doses were prescribed for use in the treatment of depression.[30] Like synthetic antidepressants, St. John's wort extract needs 2 to 4 weeks to develop its mood elevating effects.[31] And while it is considered to be safe with no apparent side effects, it should not be taken with other psychoactive drugs. When consumed in large amounts, it has been associated with photosensitivity in animals; however, photosensitization does not usually occur when used within its recommended dosage range (0.5 to 3.0 mg hypericin/day).[30]

St. John's wort contains numerous compounds with documented biologic activity.[30] Many researchers consider its effects to be due to a variety of constituents rather than any single component. These include hypericin, pseudohypericin, quercetin, hyperin, hyperforin, and xanthones. Continued research is needed to identify the constituents most responsible for St. John's activity so that preparations can be optimally standardized. The current procedure of standardizing to hypericin content appears to result in an active product and may be better than no standardization.[30]

St. John's has been tested in more than 3,000 patients against placebo and various active medications. Researchers from Germany and the U.S. recently published a meta-analysis of 23 randomized trials of extracts of St. John's wort with a total of 1,757 outpatients with mild to moderately severe depressive disorders.[32] Comparisons were made of St. John's wort alone, in combination with other plant extracts, to placebo, and/or a standard antidepressant. Twenty of the 23 trials were double-blind, one was single-blind, and two were open. Most were 4 to 8 weeks in duration and the total extract dose ranged from 300 to 1,000 mg/day (0.4 to 2.7 mg hypericin).

In 13 studies comparing a single St. John's wort preparation with placebo, 55.1% of patients receiving the herb improved, compared with 22.3% responding to placebo.[32] In the comparisons to standard antidepressants in 3 trials with single St. John's wort preparations and 2 trials with combinations (St. John's wort and *Valeriana*), 63.9% of patients responded to single preparations compared with 58.5% to standard antidepressants and 67.7% responded to combination extract products compared with 50% to standard antidepressants.

The researchers concluded that "*Hypericum* extracts were significantly superior to placebo and similarly effective as standard antidepressants" while producing fewer side effects (19.8 % vs. 35.9%).[32] While some of these studies were flawed and there is a lack of long-term studies, St. John's wort definitely shows promise in the treatment of mild to moderate depression. The evidence suggests that St. John's wort is more effective than placebo for the treatment of depressive disorders; however, evidence is inadequate to establish whether St. John's wort is as effective as other antidepressants. Studies are also needed for severely depressed patients, as are long-term studies to assess the risk of relapse and emergence of latent side effects.[31]

The mechanism of action for St. John's for treating depression is unknown, although there are several theories:[32]

- Hypericin and pseudohypericin may act on immune cells that secrete chemicals that cross the blood-brain barrier.
- St. John's either lowers levels of cortisol or acts on GABA receptors on brain cells.
- Hyperforin, another compound found in the herb, may increase brain levels of serotonin.
- St. John's wort extract may reduce cytokine expression (interleukin-6), the hypothesis being that interleukins can induce depression in susceptible individuals.

It is important to choose a St. John's wort preparation standardized to a level of hypericin that permits a daily dose of approximately 2.7 mg hypericin. To be consistent with the form used in clinical trials, the preparation should include all of the other naturally occurring substances that are found in St. John's wort and not just purified hypericin.

• Other Herbs

There are numerous plants in addition to St. John's wort that have been identified in ancient herbal texts from around the world to "settle the spirit," "lift the mood," and "clear the mind." Several of these herbs have been found to possess potent naturally occurring chemicals that support these traditional observations by influencing various organ systems that play a role in mood, anxiety, and mental function. These include salvia root *(Salvia miltiorrhiza)*, rosemary herb *(Rosemarianus officianalis)*, lavender *(Lavendula spp.)*, California poppy *(Eschscholzia californica)*, licorice root *(Glycyrrihiza spp.)*, and jujube seed *(Zizyphus spinosa)*.[33-35] For example, jujuboside, one of the active ingredients of jujube seed, has been found to possess sedative and tranquilizing properties and protopine, found in California poppy, is an alkaloid found to act as a sedative and muscle relaxant.[33]

In traditional Chinese medicine, managing emotional and mental problems involves choosing herbs that nourish the heart. It is interesting to note that two herbs frequently used in traditional Chinese medicine to enhance mood, salvia root and jujube seed, have also been found to influence the cardiovascular system.[34] Because poor circulation, particularly evident in the elderly, can contribute to depression, herbs such as hawthorn berry *(Crataegua pinnatifida)* and *Ginkgo biloba* are useful because they increase blood flow to the brain.[33]

The addition of these herbs can enhance the targeted antidepressant effect of St. John's wort by supporting multiple organ systems within the body, such as the adrenal glands, liver, cardiovascular system, and selected neurotransmitter functions.

REFERENCES

1. Stokes PE. Current issues in the treatment of major depression. *J Clin Psychopharmacol* 1993;13(suppl 2):2s-9s.
2. Mendels J. The acute and long-term treatment of major depression. *Intl Clin Psychopharmacol* 1992;7(suppl 2):21-29.
3. Smith KA, Fairburn CG, Cowen PJ. Relapse of depression after rapid depletion of tryptophan. *Lancet* 1997;349:915-19 .
4. Pajer P. New strategies in the treatment of depression in women. *J Clin Psychiatry* 1995;56(suppl 2):30-37.
5. Lesseig DZ. Primary care diagnosis and pharmacologic treatment of depression in adults. *Nurse Practitioner* 1996;21:72-76.
6. Berkow R, editor. The Merck Manual of Diagnosis and Therapy vol. 1. 15th ed. Rahway (NJ): Merck 1987. p 1125-92.
7. Costarella L. Naturopathic specific condition review: depression. *Protocol J Botan Med* 1996;2:62-64.
8. Leifer A. Allopathic specific condition review: depression. *Protocol J Botan Med* 1996;2:58-61.
9. Blier P, de Montigny C. Current advances and trends in the treatment of depression. *TiPS* 1994;15:220-26.
10. Leonard BE. New approaches to the treatment of depression. *J Clin Psychiatry* 1996:57(suppl 4):26-33.
11. Young SN. The use of diet and dietary components in the study of factors controlling affect in humans: a review. *J Psychiatr Neurosci* 1993;18:235-44.
12. Abou-Saleh MT, Coppen A. The biology of folate in depression: implications for nutritional hypotheses of the psychoses. *J Psychiat Res* 1986;20:91-101.
13. Werbach MR. Nutritional Influences on Mental Illness. Tarzana (CA): Third Line Pr; 1991. p 123-151.
14. Moller HJ, Volz HP. Drug treatment of depression in the 1990s. *Drugs* 1996;52:625-38.
15. Hale AS. Recent advances in the treatment of depression. *Br J Hosp Med* 1996;55:183-6.
16. Crellin R, Bottiglieri T, Reynolds EH. Folates and psychiatric disorders. *Drugs* 1993;45:623-636.
17. Di Palma C, Urani R, Agricola R, et al. Is methylfolate effective in relieving major depression in chronic alcoholics? A hypothesis of treatment. *Curr Ther Res* 1994;55:559-68.
18. Bottiglieri T. Folate, vitamin B12, and neuropsychiatric disorders. *Nutr Reviews* 1996;54:382-390.
19. Carney MWP, Chary TKN, Laundy M, et al. Red cell folate concentrations in psychiatric patients. *J Affect Disorders* 1990;19:207-13.
20. Santhosh-Kumar CR, Hassell KL, Deutsch JC, et al. Are neuropsychiatric manifestations of folate, cobalamin and pyridoxine deficiency mediated through imbalances in excitatory sulfur amino acids? *Medical Hypotheses* 1994;43:239-44.
21. Levitt AJ, Joffe RT. Vitamin B12 in psychotic depression. *Br J Psychiatry* 1988;153 (letter):266-67.
22. Abou-Saleh MT, Coppen A. Serum and red blood cell folate in depression. *Acta Psychiatr Scand* 1989;80:78-82.
23. Ghadirian AM, Ananth J, Engelsmann F. Folic acid deficiency and depression. *Psychosomatics* 1980;21:926-29.
24. Fava M, Borus JS, Alpert JE, et al. Folate, vitamin B12, and homocysteine in major depressive disorder. *Am J Psychiatry* 1997;154:426-28.
25. Godfrey PSA, Toone BK, Carney MWP, et al. Enhancement of recovery from psychiatric illness by methylfolate. *Lancet* 1990;336:392-95.
26. Young SN, Ghadirian AM. Folic acid and psychopathology. *Prog Neuro-psychopharmacol. & Biol Psychiat* 1989;13:841-63.
27. Belmaker RH, Bersudsky Y, Agam G, et al. How does lithium work on manic depression? Clinical and psychological correlates of the inositol theory. *Annu Rev Med* 1996;47:47-56.
28. Kofman O, Belmaker RH. Biochemical, behavioral, and clinical studies of the role of inositol in lithium treatment and depression. *Biol Psychiatry* 1993;34:839-52.
29. Snow JM. *Hypericum perforatum* L. (Hyperiaceae). *Protocol J Botan Med* 1996;2:16-21.
30. Upton R, ed. St. John's Wort, *Hypericum perforatum*. American HerbalPharmacopoeia July 1997.
31. De Smet PA, Nolen WA. St. John's wort as an antidepressant. *BMJ* 1996;123:241-242.
32. Linde K, Ramirez G, Mulrow CD, et al. St. John's wort for depression-an overview and meta-analysis of randomised clinical trials. *BMJ* 1996;313:253-58.
33. Duke JA. Handbook of Biologically Active Phytochemicals and Their Activities. Boca Raton (FL): CRC Pr 1992.
34. Bensky D, Gamble A. Chinese Herbal Medicine: Materia Medica. Washington: Eastland Pr; 1993.
35. Liao JF, Jan YM, Huang SY, et al. Evaluation with receptor binding assay on the water extracts of ten CNS-active Chinese herbal drugs. *Proceedings of the National Science Council* 1995;19:151-58.