

Depression

**It's not a disease; it's something we all
suffer from occasionally**

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An Alternative-
Doctor Report

DEPRESSION: NOT JUST A DISEASE, IT'S SOMETHING WE ALL SUFFER FROM OCCASIONALLY

by Dr Keith Scott-Mumby MB ChB, MD, PhD

We all feel depressed from time to time. Almost everyone has experienced upset and used the expression "I am depressed". However this is usually a transient state of affairs.

Depression is a clinical condition and more protracted and severe than everyday feelings of "the blues". The patient's deep gloom and sense of helplessness can be so crippling at times that he or she may consider the possibility of ending it all. In the USA over 32,000 suicide attempts were successful in 2004, making this the 10th cause of death (3rd in young people).

This appalling toll tells us all too clearly that conventional treatment for depression has a long way to go. On the larger social scale there have been a number of spectacular incidents in which a clinically depressed patient ran amok and committed multiple murders, before ending their own life (Columbine, 1999 and the Virginia Tech slayings, 2007). Here we seem to have a remarkable modern development of "suicide with multiple mortality".

It is even possible to suspect in these cases that ineffective medication, with deleterious and complex side effects, was actually the *trigger* to the murderous outrage. It is time to look beyond pharmaceutical tweaking of brain chemicals and consider what natural remedies have to offer. There are also many physical causes of depression which may lead to a full and satisfying recovery, once these are identified and corrected. This major **Alternative Doctor** overview points to many therapeutic avenues, showing that depression is a complex and multi-factorial problem and not merely a neurotransmitter shortage.

Classification

Depression is not generally categorized by severity but by presentation. Sub-categories include seasonal affect disorder (SAD) or the “winter blues”, pre-menstrual depression (pre-menstrual dysphoric disorder or PMDD), dysthymia (a milder form of depression) and post-partum depression (after giving birth).

Two variants of major depression are very important: unipolar depression and bipolar disorder. Bipolar disorder is a condition in which the sufferer cycles through bouts of mania or hyper-agitation, followed by inertia and deep depression. The switches can be very dramatic and unpredictable, making this condition very difficult to live with for both patients and family. In its lesser form, the patient may only be aware of racing thoughts, fatigue and insomnia, loss of appetite and sexual dysfunction, rather than depression *per se*.

Unipolar depression is so called to distinguish it from bipolar disorder and it does not have the hyper-excitabile manic phase. More commonly it is known as major depression or just “depression”. This booklet concentrates mainly on unipolar depression. However it should be said that any type of depression will benefit from adopting some of the effective holistic approaches described here. Indeed, even if you only have the milder “blues” these are very good strategies that will soon have you back feeling on top of the world, with energy to spare!

Conventional therapy and its shortcomings

Did you know that among those who seek professional help for depression, less than half of patients will be correctly diagnosed as depressive? [Agency for Healthcare Policy and Research. Depression in Primary Care. Vol. 1. Detection and Diagnosis. Publication 93-0550. Rockville, Md: US Dept of Health and Human Services; 1993.] Of those who are diagnosed with depression, only one half will receive any form of therapy for their illness.[Lepine JP, Gastpar M, Mendlewicz J, et al. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). Int Clin Psychopharmacol.

1997;12:19-29.] Finally, among those who do receive treatment, only 25% will receive an adequate antidepressant dose and duration of treatment.[Katon W, Schulberg H. Epidemiology of depression in primary care. *Gen Hosp Psychiatry*. 1992;14:237-247.]

These figures are bound to be conservative, since many depressed people do not admit to their problem openly.

For decades the main treatment was electro-convulsive therapy (ECT). It remains the treatment of choice for hospitalized patients for severe depression. However it is far from satisfactory, often causing personality changes and memory loss. Moreover patients sometimes injure themselves during the seizures.

In the 1950s a whole class of anti-depressant drugs was developed called the monoamineoxidase inhibitor (MAOIs for short), closely followed by the tri-cyclic anti-depressants (TCAs). While sometimes effective, both these classes of drugs cause troublesome side effects and have complex, potentially fatal, drug interactions. Their mode of action is to block the breakdown of neurotransmitters like serotonin and norepinephrin, which are known to enhance mood.

The latest major class of drugs—the selective serotonin re-uptake inhibitors (SSRIs)— act similarly, by preventing the natural re-absorption of serotonin by the nerve endings. This leads to pooling and more available serotonin. SNRIs act the same way with norepinephrin. Fluoxetine (Prozac) was the first SSRI. It has been joined by paroxetine (Paxil®), sertraline (Zoloft®) and numerous others, several of which have become virtual household names.

SSRIs and SNRIs are far from perfect and also have troubling side effects but are today considered the drugs of choice for depression.

Several mechanisms of depression

The undoubted success of SSRIs has led to the postulation that depression is mainly a deficiency of the monamine neurotransmitters serotonin and/or noepinephrine—the so-called monoamine theory (Hou

C et al 2006; Prange AJ et al 1974). It has emerged that this narrow view is far too simplistic.

One of the great surprises has been the discovery that depression has a pronounced inflammatory component. Increased levels of inflammatory proteins, such as interleukin one-beta (IL-1b) and tumor necrosis factor-alpha (TNF-a), suggest that low-grade, body-wide inflammation accompanies depression. Moreover, levels of these inflammatory markers correlate well with the severity of depression. [[Psychosom Med. 2007;69:217-224.](#)]

One postulated mechanism is that inflammatory cytokines activate an enzyme called IDO (indoleamine 2,3-dioxygenase), which primarily breaks down serotonin and tryptophan. This is the exact opposite of the beneficial action of SSRIs [[Mol Psychiatry. 2007 Apr 24; epub ahead of print](#)].

A recent study carried out at Tel Aviv University in Israel is the first published report of deliberately induced inflammation causing signs of experimental depression in mice. Significantly, this effect was blocked by the administration of the SSRI fluoxetine (Prozac®), which may suggest an entirely different pathway for the mode of action of SSRIs. [[Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. Arthritis Rheum. 2007 Mar;56\(3\):938-48](#)].

Omega-3 fatty acids are an essential dietary factor in combating inflammation. Patients with the lowest levels of essential omega-3 fatty acids tend to be the most severely depressed, while healthy control subjects are more likely to have normal levels of omega-3s, as measured in red blood cell membranes. [[Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. J Affect Disord 1998 Mar; 48\(2-3\):149-55](#)].

Alternative Doctor recommendations for lowering inflammation.

Without doubt the most important anti-inflammatory supplements are omega-3 fatty acids EPA and DHA (eicosapentanoic acid and docosahexaenoic acid). In 2006, researchers analyzed results from six

published studies on depression and omega-3 fatty acids. They found that omega-3 fatty acids can significantly reduce symptoms of depression among adults (Williams AL et al 2006). Omega-3s are best obtained from marine sources and true grass-fed beef. Vegetarians will need plant sources, such as flaxseed. Dose: 1000- 2000 mgms daily.

[See LE Magazine December 2003: Omega-3 Fatty Acids Vital to a longer, healthier life for information on omega-3s and brain function health.](#)

DHEA, an important hormone precursor (see below), also has anti-inflammatory properties. Add nettle leaf extract and vitamin K. If blood tests still show that you still have high levels of inflammatory cytokines, I suggest you should consider 400 mg to 800 mg a day of pentoxifylline (PTX) or proprietary Enbrel (if you can afford it).

Note that omega-6 fatty acids, although “essential” by name, are far too prevalent in modern diets and considerably outweigh omega-3s. This creates a relative omega-3 deficiency.

According to a recent study, depressed people have lower levels of omega-3 fatty acids compared with the pro-inflammatory omega-6 fatty acids, and the severity of symptoms correlated with the ratio of omega-6 to omega-3 fatty acids. Moreover inflammatory markers — interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α) — showed a direct correlation with the omega-6:omega-3 ratio. [[Psychosom Med. 2007;69:217-224](#)].

Studies among prison inmates by Bernard Gesch in the UK report that aggression and violence is reduced, as well as mood improved, by supplementation with omega-3 fatty acids. Apparently the chance of being murdered is 30 times greater in countries with a low fish consumption, according to Joseph Hibbeln MD, working at the US National Institutes of Health (NIH) [[Feed Your Brain, Ode Magazine, Jurriaan Kamp, vol 5 issue 7, pp 40- 45](#)].

To lower you omega-6 intake, cease eating manufactured food and rely instead of healthy wholefoods, such as fruit, vegetables, salads and fish.

Consider also enzyme formulas which contain bromelain and papain, possibly with pancreatic extract. These digestive enzymes dissolve and

clean up pro-inflammatory chemical compounds.

See LE Magazine January 2002: [Protecting Against Inflammatory-Related Disease](#) for a comprehensive overview of anti-inflammatory supplements.

Your Heart Speaks Your Mind

C-reactive protein is another inflammatory protein found at higher levels in depressed persons. It is also commonly found in patients with cardiovascular disease, pointing to some as-yet-unfathomed connection between depression and the heart. [[Musselman DL, Miller AH, Porter MR, et al. Higher than normal plasma interleukin-6 concentrations in cancer patients with depression. Am J Psychiatry. 2001 Aug;158\(8\):1252-7](#) and [Corti R, Hutter R, Badimon JJ, Fuster V. Evolving concepts in the triad of atherosclerosis, inflammation and thrombosis. J Thromb Thrombolysis. 2004 Feb;17\(1\):35-44. \]](#)

An even more explicit association with cardiovascular disease was revealed by a recent study showing that depressive states can actually lead to thickening of the arterial linings and hence reduced blood flow. Moreover this study specifically ruled out other negative emotions, anxiety, hostility, and anger as having the same effect on cardiovascular health. [[Arch Gen Psychiatry. 2007;64:225-233, 242-249](#)]

Another new report reveals that heart failure patients with highest levels of the cytokine TNF-1 have an almost 5-fold risk for depression. [[American College of Cardiology 56th Annual Scientific Sessions: Abstract 1004-61. March 24 – 27, 2007](#)].

Homocysteine

Homocysteine, a general marker for ill health, is also indicative of heart disease. It basically denotes a failure of the healthy re-methylation, a process known to repair DNA and prevent aging. Up to 50% of depressed people have homocysteine levels that are significantly above normal, considered to be greater than 10 millimoles per liter (mmol/L) of

blood. [Bottiglieri T, Laundry M, Crellin R, Toone BK, Carney MW, Reynolds EH. Homocysteine, folate methylation, and monoamine metabolism in depression. *J Neurol Neurosurg Psychiatry*. 2000 Aug;69(2):228-32 and Fava M, Borus JS, Alpert JE, Nierenberg AA, Rosenbaum JF, Bottiglieri T. Folate, vitamin B12, and homocysteine in major depressive disorder. *Am J Psychiatry*. 1997 Mar;154(3):426-8].

Levels above 10 mmol/L are considered unsafe and indicate a risk of serious cardio-vascular and neurological damage. It is recommended to aim for a level of 8 mmol/L or less. 6 mmol/L is better. One study found each 3-unit increase in homocysteine caused a 35% increase in heart attack risk (see the *American Journal of Epidemiology* 1996; vol 143, no. 9 845-859).

Alternative Doctor recommendations are as follows:

Homocysteine levels can be lowered by a number of nutrients, some of which (especially S-adenosyl-L-methionine, or SAME) have been found to improve depression independently. A recent Canadian review elaborated extensive evidence for the fact that SAME provides a mechanism for removing toxic homocysteine.

[*Biofactors*. 2006;26(1):45-57].

Take 400 to 1200 mg of SAME daily without food.

B6, B12 and folic acid also lower homocysteine levels. Take a full complement of B vitamins (including at least 1000 micrograms (mcg) vitamin B12, 250 milligrams (mg) vitamin B6, and 800 mcg of folic acid daily

Zinc acts in concert with vitamin B6 to promote remethylation of homocysteine to methionine. Take 15 to 30 mg zinc daily.

Other nutrients which benefit homocysteine levels include anti-oxidants (selenium), sulfur donors (cysteine) and methyl donors (trimethyl glycine or TMG). Take 100 mcg selenium, N-acetyl-cysteine 600 mg (in capsule form) one to two times daily on an empty stomach and/or 2 to 4 grams (g) TMG daily

What remains unclear to date is whether lowering homocysteine levels has any benefit in reducing depression scores. Nevertheless, I consider it prudent to keep homocysteine levels as low as possible, certainly less than 8 mmol/L.

See also [LE Magazine October 2006: Homocysteine as a Risk Factor for Disease](#), for a comprehensive overview.

The cortisol connection

Cortisol levels are consistently elevated in depressed subjects, due to over-stimulation of the hypothalamic-pituitary-adrenal axis, which regulates cortisol secretions. Concomitant secretions of vasopressin increases this effect [[Ageing Res Rev. 2005 May;4\(2\):141-94](#)].

Vasopressin thus reinforces depression negatively and is felt to be the probable trigger for suicide. Oxytocin (the "love or bonding hormone"), on the other hand, lowers cortisol [[Journal of Clinical Endocrinology & Metabolism, 1984; vol 58, pages 105-109](#) and [Biological Psychiatry Volume 54, Issue 12, 15 December 2003, Pages 1389-1398](#)].

This gives some credence to the old saying that "It is better to have loved and lost than never to have loved at all".

However depression may not simply be a response to stress but be related to some fundamental dysfunction of the HPA axis. In depressed patients cortisol levels peak in the afternoon, whereas they peak around 8.00 am in a normal individual.

A recent study ([published March 2007](#)) studied patients diagnosed with unipolar depressive disorder, some recovered, some still depressed. Cortisol and ACTH levels were measured and clearly abnormal in the both groups, compared to controls. What is revealing is that the recovered group also scored badly, showing their HPA axis had remained abnormal, even while mood was restored This points to some underlying malfunction of the HPA axis that has yet to be clarified. [[Prog Neuropsychopharmacol Biol Psychiatry. 2007 Mar 7; ePub, ahead of print](#)]

While it is not established that cortisol levels are causative in depression, it makes sense to attempt to reduce the stress response. Meditation, because of its deeply introvertive action, may not be appropriate for depression cases. But therapeutic massage, aromatherapy with essential oils, moderate exercise, hobbies, laughter and social support are all tried and proven methods of lowering stress levels.

A study, which was reported by Valencia Porter, MD, of the Scripps Center for Integrative Medicine (SCIM) in La Jolla, California, and colleagues involved a review of the charts of 569 patients who had been enrolled in the "Healing Hearts" program—a 6-month, integrated rehabilitation program incorporating yoga, exercise, stress management, and nutrition counseling. The improvements were surprisingly robust, according to Dr Porter. [\[ACPM 2007 Annual Meeting: Poster 16. Presented February 22, 2007\].](#)

A number of recognized supplements could be helpful in reducing overall stress and creating a "feel good" sensation:

Phenylethylamine (PEA). This compound is an endogenous neuroamine and has been called the "love molecule". PEA unquestionably increases mood and leads to sustained relief of depression in a significant number of patients. PEA works as rapidly as amphetamine but does not produce tolerance. [\[Sabelli H, Fink P, Fawcett J, et al. Sustained antidepressant effects of PEA replacement. J Neuropsychiatry 1996;8:168–. 71\].](#) It is found in chocolate but highest concentrations are found in the blue-green algae *Aphanizomenon flos-aquae* (AFA). Phycocyanin, the blue pigment in AFA, is a natural selective COX-2 inhibitor with strong anti-inflammatory properties, which suggests it may also act directly against the inflammatory component of depression.

Recommended dose: aim for about 800 mgms of AFA.

Phenylalanine. This is a related compound and a number of studies have shown it to be effective against depression. It leads to an increase in the body's natural PEA levels (measured by urinary excretion). Side effects are few and include mild headache, low blood pressure, and agitation. Phenylalanine may also help regulate disordered glucose

metabolism, another aspect of depression (see next). [[Journal of Orthomolecular Psychiatry \(Regina\) 5\(3\):199-202, 1976](#) and [Biological Psychiatry 10\(2\):235-239, 1975](#)]

Take 200- 500 mg daily of phenylalanine.

S-Adenosyl methionine (S-AMe)

S-AMe (pronounced sammy) has long been known as an effective antidepressant in its own right and is widely prescribed by doctors in Europe. Clinical trials comparing both oral and intramuscular forms of S-AMe to tricyclic antidepressants show S-AMe to be as effective as tricyclic antidepressants in reducing the symptoms of depression (Mischoulon D et al 2002; Pancheri P et al 2002). S-AMe is associated with fewer adverse events (Pancheri P et al 2002) and is better tolerated than conventional antidepressants (Delle CR et al 2002).

[See LE Magazine June 2003: A New Era for S-AMe for more details of this amazing health-giving nutrient.](#)

Take 400 to 1200 mg of S-AMe daily without food.

Tryptophan and 5-hydroxytryptophan (5HT). Available as dietary supplements, these two substances are immediate precursors to serotonin. In some countries, tryptophan is licensed as an antidepressant (Murphy SE et al 2006). More study is needed on the use of these supplements in depression.

Take 500 to 1000 mg of tryptophan once or twice daily on an empty stomach

The glucose connection

The link between obesity and depression has been long known. "Comfort eating" is a laymen's concept that has all but crept into the medical canon.

A 2007 study indicated women with high levels of depressive symptoms have an increased risk of developing metabolic syndrome (obesity and

insulin resistance, among other factors) [[Diabetes Care. 2007;30:872-877](#)]. Now a recently published 10-year study has shown that older adults who show a high level of depressive symptoms, or experience a significant deterioration in mood, are more likely to develop type 2 diabetes. [[Arch Intern Med. 2007;167:802-807](#)]

An almost contemporaneous study implied that successful lowering of depression scores had no beneficial effect on glycemic control. [[Psychosom Med 2007;69:235-241](#)]. However this is contradicted by a somewhat earlier study, which showed that depression improvement can produce better glycemic control, independent of favorable changes in weight and diabetes self care. [[Diabetes Care 2007;30:459-466](#)].

Recommendations:

The simplest corrective intervention is with knife and fork. Patients should limit their carbohydrate intake to a maximum of 120 grams daily and this to be taken in the form of complex carbs (whole grain, pulses etc). The rest of the diet should consist of vegetables, fruits (2 pieces), salads, fish, fowl and lean meat—the Mediterranean diet.

Chromium has long been known to be outstanding for regulating glucose levels. The recommended adult dose is 400 mcg daily. Other supplements to consider are:

- DHEA: 10-50 mg per day to start (men), 10-30 mg per day to start (women); assess effect via repeat blood test
- Omegas-3s: 1000- 2000 mgm daily
- Lipoic acid: 150 mg once or twice daily
- Mixed tocopherols (vitamin E): 400 IU twice daily with mixed tocotrienols (75 mg twice daily)
- Vitamin A: 5000 IU per day, with mixed carotenoids (for example, lutein 5000 mcg, lycopene 3000 mcg, and zeaxanthin 360 mcg) daily
- Pycnogenol: 200 mg daily

The melatonin connection

The intimate relationship between depressive disorders and biological rhythm disturbances has long been known. Major depression sufferers experience their worst feelings in the early hours of the morning. One major component in diurnal rhythm regulation in humans is the melatonin axis and its close connections with serotonin and noradrenalin receptors. Measurement of melatonin either in saliva or plasma have shown significant alterations in melatonin secretion in depressive patients during the acute phase of illness. [[World J Biol Psychiatry. 2006;7\(3\):138-51](#)].

Whole new therapeutic possibilities have opened up with the introduction of agomelatin, a novel antidepressant with direct agonist activity at the melatonin receptors, and a selective antagonist action at the serotonin receptor. It has no measurable affinity to any other known receptors.

In randomized and controlled clinical trials in humans agomelatin appears to be an effective antidepressant, comparable to standard SSRI/SNRI drugs, with excellent safety and tolerability profile [[Expert Rev Neurother. 2006 Nov;6\(11\):1595-608](#).[Click here to read](#)]. Sleep is improved and agomelatin causes significantly less sexual dysfunction than a reference SNRI. No discontinuation symptoms have been observed upon abrupt withdrawal. [[Neuropsychopharmacol Hung. 2006 Oct;8\(3\):105-12](#)].

See below for recommendations for self-dosing with melatonin.

Hormonal factors contributing to depression.

Thyroid. Without doubt the main hormonal imbalance missed in depressed patients is thyroid insufficiency. It has been estimated that at least 10- 15% of people suffering from depression are undiagnosed hypothyroid [[Hickie I, Bennett B, Mitchell P, Wilhelm K, Orlay W. Clinical and subclinical hypothyroidism inpatients with chronic and treatment-](#)

resistant depression. *Aust N Z J Psychiatry* 1996;30(2):246-52.]. The real figure must arguable be far higher, since few depressed patients are investigated for hormonal dysfunction.

Low T3 (the most powerful thyroid hormone) is associated with resistant depression and a tendency to relapse quickly. [*Jackson IM. The thyroid axis and depression. *Thyroid* 1998;8(10):951-6. *Joffe RT, Marriott M. Thyroid hormone levels and recurrence of major depression. *Am J Psychiatry* 2000;157:1689-1691]. Conversely a series of open studies seemed to suggest that (T3) has a beneficial effect in a majority of patients with depression refractory to tricyclic therapy [*Archives of General Psychiatry* 1993; 50(5):387-93 and *Journal of Clinical Psychiatry* 1993; 54(2):47-54]. However, according to a 2005 study, T3 did not enhance SSRI efficacy (paroxetine) [Appelhof BC, Brouwer JP, van Dyck R, Fliers E, Hoogendijk WJ, Huyser J, Schene AH, Tijssen JG, Wiersinga WM. Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. *J Clin Endocrinol Metab* 2004;89:6271-6].

Testosterone. The male menopause or andropause is just as significant an event for men as for women and symptoms are remarkably similar.

Testosterone levels should be checked in depressed men of any age. Studies repeatedly show low levels of testosterone in depressed men and this was re-inforced yet again by a recent (2006) Canadian study which found middle-aged men with depression have reduced levels of bioavailable testosterone as well as lower circulating total testosterone compared with their counterparts without depression.

[*Psychoneuroendocrinol.* 2006;31(9):1029-1035].

Carnitine is a supplement that may be equal to testosterone in its ability to improve sexual function, boost low moods, increase energy, and promote weight loss through its effect on fat and glucose metabolism. A dose of 2000 mg per day of acetyl-L-carnitine has been found effective in most studies [Cavallini G, Caracciolo S, Vitali G, Modenini F, Biagiotti G. Carnitine versus androgen administration in the

treatment of sexual dysfunction, depressed mood, and fatigue associated with male aging. *Urology*. 2004 Apr;63(4):641-6].

Estrogen. Estrogen is also linked to depression. Women using estrogen replacement therapy to alleviate menopause symptoms appear to experience reduced depression (Miller KJ et al 2002). In some older women being treated for depression, estrogen replacement therapy may actually improve the effects of conventional antidepressants (Schneider LS et al 2001).

Estrogen is thought to produce its antidepressant effects by regulating serotonin in the central nervous system (Joffe H et al 1998; Rubinow DR et al 1998). Estrogen is also thought to reduce monoamine oxidase activity, increasing available levels of neurotransmitters.

Progesterone. This normally very positive and helpful hormone has a paradoxical reverse effect in depression and should be administered as a supplement only with extreme caution. Progesterone and even more so synthetic progestogens increase monoamine oxidase activity [*Molecular Human Reproduction* 2006 12(12):749-754; doi:10.1093/molehr/gal082]. This action is probably the explanation behind premenstrual dysphoric disorder (progesterone predominates over estrogen in the latter half of the menstrual cycle).

DHEA. DHEA is probably the most abundant steroidal hormone substance in the body. Levels are especially high in the brain. DHEA is the biochemical precursor to a number of other hormones, notably estrogen, progesterone and testosterone, which may explain in part why it benefits depressed patients. [See also *Life Extension Magazine August 2002: Grumpy No More: Testosterone Deficiency & Depression Does DHEA Raise The Levels Of Bioavailable Testosterone In Men?* for more discussion]

In a randomized, placebo-controlled, double-blind study that lasted for six years, researchers tested 90 mg DHEA daily for 3 weeks and 450 mg/d for 3 weeks as a monotherapy for both mild and severe depression. They found that DHEA therapy resulted in a significant

improvement in symptoms, compared with placebo (Schmidt PJ et al 2005).

DHEA has been shown to effectively lower evening cortisol levels and improve mood, by a double-blind placebo-controlled trial.

[[Psychopharmacology \(Berl\)](#). 2005 Oct 18;:1-11 Psychobiology Research Group, School of Neurology, Neurobiology and Psychiatry, University of Newcastle upon Tyne, Newcastle upon Tyne, UK]

Dose: 10-50 mg per day to start (men), 10-30 mg per day to start (women); and if possible to assess effect via repeat blood test. Note that DHEA often causes greasy facial skin in women and dosage may need to be reduced accordingly.

Pregnenolone. The happy hormone. Pregnenolone levels in the healthy brain are some 10 times greater than DHEA levels. Patients suffering from depression have been found to have pregnenolone levels less than half those found in nondepressed persons. These decreased levels of pregnenolone have been found in both unipolar and bipolar depression (the manic-depressive disorder). In job-performance studies, subjects reported better mood when taking pregnenolone. Pregnenolone seems to have a pleasant stimulatory effect on the brain, without overstimulation.

Dose: 5 or 10 mgms daily.

Melatonin. Melatonin is a confusing element in the overall picture of depression. Successful treatment of unipolar depression with the melatonin agonist agomelatin has already been noted above. But melatonin contributes significantly to bipolar depression and seasonal affect disorder (SAD). Both these depressive states are benefited from whole spectrum light, which suppresses melatonin secretion. [[World J Biol Psychiatry](#). 2006;7(3):138-51]. Yet whole spectrum light does not benefit unipolar disorder [[Acta Psychiatr Scand](#). 1997 Nov;96(5):385-94].

Rat studies showed that melatonin at a concentration of 0.5 mg/kg had a similar antidepressant effect to clomipramine as 50 mg/kg. To further

reinforce this finding the simultaneous injection of the non-selective melatonin antagonist, luzindole, abolished the effect [Eur Neuropsychopharmacol. 2006 Oct;16(7):538-45. Epub 2006 Mar 9].

Nevertheless, melatonin does cause lethargy and low mood in some healthy individuals. Therefore it should be supplemented cautiously in depression. Start with 0.5 – 1.00 mgm and rise in 1 mgm increments (maximum 5 mgm).

*

NOTE: Most critical hormones are easily measured by a simple saliva test from laboratories such as Diagnos-techs (www.diagnos-techs.com). It is important to measure all hormones and when supplementing, even with so-called bio-identical hormones, to bear in mind that they all interact with each other. The aim is to restore hormone levels to those of a healthy young adult.

Nutrient deficiencies

Nutrient deficiencies have long known to provoke or exacerbate depression. Any vitamin deficiency will impact general health but the B complex group (including folate) are particularly important for healthy brain function by regulating energy metabolism, assisting in the production of chemicals that affect mood, and contributing to the myelin sheath surrounding and protecting nerves. B-vitamin deficiencies may therefore impair memory and increase anxiety, confusion, irritability, and depression. [Morris MC, Evans DA, Bienias JL, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J Neurol Neurosurg Psychiatry. 2004 Aug;75(8):1093-9.]

B1 (Thiamine) is vital for the functioning of healthy nerve tissue. The recommended daily allowance is 1.5 mgms. But infections, large volumes of urine, alcohol, antacids and HRT all increase requirements.

B3 Niacin. This vitamin has long been known to be helpful in depression but citations are remarkably lacking. A 2003 study showed that niacin was a potent inhibitor of proinflammatory cytokines, which

may indicate a possible mode of action [[Clin Exp Immunol. 2003 Jan;131\(1\):48-52](#)]

Vitamin B6 (pyridoxine). In 2005, a team of researchers from Yale University examined all the published studies on vitamin B6 and depression. Although the researchers did not find evidence of benefits from vitamin B6 treatment in the results of all the studies, they did find that premenopausal women suffering from depression benefited from vitamin B6 (Williams AL et al 2005). B6 is known to help lower homocysteine levels.

Vitamin B12 (cobalamin). Deficiency in vitamin B12 has been cited as a risk factor for developing depression (Gottfries CG 2001) and is associated with increased homocysteine (Parnetti L et al 1997; Stabler SP et al 1990). People with high vitamin B12 levels have better treatment outcomes for major depression (Hintikka J et al 2003). Vitamin B12 supplementation is important for depressed individuals, particularly older patients, in whom low vitamin B12 levels are common (Lindeman RD et al 2000; Penninx BW et al 2000).

Folic acid. Treatment resistant depression has been linked to low blood levels of folic acid. Folic acid deficiency causes high homocysteine blood levels. Folate-deficient people are also more likely to be deeply depressed and for longer periods. [[Morris MS, Fava M, Jacques PF, Selhub J, Rosenbert IH. Depression and folate status in the US population. Psychother Psychosom. 2003 Mar;72\(2\):80-7](#)]. This variety of depression responds poorly to antidepressant medication, but naturally does respond to folic acid. Because relapse is associated with low serum folate, it is important to maintain folate supplementation for a year following a depressive episode (Morris MS et al 2003).

Other vitamins. Vitamin C and vitamin E. Vitamin C is a well-known antioxidant. Studies indicate that levels of vitamin C are lower in people with depression than in those without depression (McKee T et al 1999a; Khanzode SD et al 2003). Ascorbic acid indirectly inhibits oxidative stress by enhancing the activity of other antioxidants, such as vitamin E (McKee T et al 1999b). Low serum levels of vitamin E are linked to major depression (Maes M et al 2000).

Magnesium. This mineral is a vital cofactor in over 300 enzyme functions in the body, many concerned with detoxification pathways and many are found in the brain. The consequences of magnesium deficiency vary from heart arrhythmias to seizures, diabetes to hypothyroidism.

Magnesium deficiency has long been known to be a causal factor in depression [Wacker WEC and Parisi AF. *Magnesium Metabolism. New England Journal of Medicine.* 1968;278(12):658-776.] One study noted that magnesium levels in cerebro-spinal fluid were low in patients who had attempted suicide and moreover correlated with levels of 5-hydroxyindoleacetic acid, a metabolite of serotonin. [Biol Psychiatry. 1985 Feb;20(2):163-71]. Another study showed that the calcium/magnesium ratio is abnormally high in depression sufferers. [Neuropsychobiology. 1999;39(2):63-70].

Magnesium deficiency is associated with increase in C-reactive protein, one of the main markers for chronic inflammation. [King D, Mainous A 3rd, Geesey M, Woolson R. *Dietary magnesium and C-reactive protein levels. J Am Coll Nutr.* 2005 Jun 24(3):166-71]. This may be yet another pathway in which magnesium helps depression scores.

Unfortunately, magnesium is very depleted in the typical Western diet. Few people reach the RDA of 400 mgms for an adult male. Magnesium is mainly found in unprocessed nuts, grains, beans, seeds and green leafy vegetables. [see also LE Magazine September 2005: How Many Americans Are Magnesium Deficient?]

Zinc. Decreased blood levels of zinc are associated with depression (Maes M et al 1994, 1997; McLoughlin IJ et al 1990), and maintaining a healthy zinc level in the brain is essential to normal brain function (Takeda A 2000).

Animal studies show that antidepressants and electroconvulsive shock treatments change zinc concentrations in areas of the brain associated with depression (Nowak G et al 1999). In an animal study, zinc was also shown to enhance antidepressant effects of imipramine, the original MAOI (Krocza B et al 2001).

Toxic burdens

Heavy Metal Toxins. As well as testing for deficiencies, the alert physician will investigate possible toxic burdens. Heavy metal poisoning is a well-recognized health problem in today's industrialized world. Toxic metal poisoning can interfere with healthy enzyme systems and this may lead to a multitude of symptoms, including depression.

The treatment is chelation. This may require an office procedure. But many available sulfur-containing food substances have chelation properties, especially garlic, kelp (seaweed) and cilantro. Chlorella, an algae, is known as a magnet for heavy metals: take 2- 6 tablets daily. Lipoic acid is also chelator and has fantastic all-round health benefits. Take 200 mgm daily of lipoic acid, in divided doses.

Zinc is a pre-cursor of metallothionein, a protein capable of chelating lead and arsenic. [Vasak, M. (2005), "Advances in metallothionein structure and functions", *J. Trace Elem. Med. Biol.*, 19 (1): page 13-17]

Food allergies. In his *Anatomy of Melancholy* (1621) Robert Burton, an English cleric noted: "Milk, and all that comes of milk, as butter and cheese, curds etc., increase melancholy." It is the first recorded recognition that food intolerance could cause depression. Since then it has become abundantly clear that many foods can and do have this selective adverse effect in intolerant individuals

It is essential that patients suffering from depression and other symptoms of mental dysfunction be investigated competently for the possibility of food reactions. The bench mark is elimination and challenge eating but there are many pitfalls in this seemingly simple procedure, which will confuse the unwary [DIET WISE, Keith Scott-Mumby MD, Timpanogos Publishers, Orem, Utah, 2007: ISBN 978-0-9768617-1-3].

- Multiple Chemical Sensitivity (MCH). Patients with multiple chemical sensitivity are known to suffer depression. They have long had to endure the scorn of the medical profession and the presumption that their sensitivities are illusory and that

depression is actually the cause of their syndrome, not the other way round.

All antioxidants, especially vitamin C, are useful detoxers. One of the most powerful antioxidants of all is glutathione. It also plays a vital role in the cytochrome P-450 oxidation pathway. Any sulfur donor help too, such as cysteine and sulfur-containing foods: garlic and brassicas.

Take Vitamin C 2 grams daily, glutathione 250 mgm daily and L-cysteine 50 mgms. These may be available as combination capsules, depending on the supplier.

It makes sense to protect the liver and kidneys, our main detox and excretion organs, against the present chemical blizzard we are all experiencing. Milk thistle (Sylimarin) is a highly effective herbal remedy known to support the liver.

Finally, the homeopathic connection.

Let's not forget the gentle healing of homeopathy. The full treatment of psychiatric symptoms can be complex and require full training as a homeopath. But there are simple options for the lay person. HEEL (www.heelusa.com and www.biopathica.com)

makes a number of useful compounds:

Ignatia-homaccord is good for the depression of grieving (Ignatia amara).

Nervo-Heel is suggested for reactive depression (exogenous) and

Psorino-Heel, supported by *Nervo-Heel* and *Ignatia-Homaccord*, for endogenous depression.

Possibly the best thought-out depression remedy is Deprex by Vaxa (www.vaxa.com).

Deprex contains remedies which help the body to naturally regulate hypothalamic activity and balance the natural production of serotonin and norepinephrine. Deprex also contains Ignatia, as well as Avina sativa.

The latter is excellent for nervous exhaustion, and sleeplessness. It also contain homeopathic lithium carbonate; lithium is the main orthodox treatment for bipolar depression.

There are several homeopathic ingredients that aid in the reduction of Depression symptoms such as: insomnia, headaches, restlessness, fatigue, changes in appetite, uncontrollable weeping, etc.

Deprex can be taken concurrently with medication but the prescribing physician should be notified as a matter of routine.

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