Primary Care Mental Health (2003) **1**: 9–16

Invited papers

Depression: the nutrition connection

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There is little doubt that the incidence of depression in Britain is increasing. According to research at the Universities of London and Warwick, the incidence of depression among young people has doubled in the past 12 years. However, whether young or old, the question is why and what can be done? There are those who argue that the increasingly common phenomenon of depression is primarily psychological, and best dealt with by counselling. There are others who consider depression as a biochemical phenomenon, best dealt with by antidepressant medication. However, there is a third aspect to the onset and treatment of depression that is given little heed: nutrition.

Why would nutrition have anything to do with depression? Firstly, we have seen a significant decline in fruit and vegetable intake (rich in folic acid), in fish intake (rich in essential fats) and an increase in sugar consumption, from 2 lb a year in the 1940s to 150 lb a year in many of today's teenagers. Each of these nutrients is strongly linked to depression and could, theoretically, contribute to increasing rates of depression. Secondly, if depression is a biochemical imbalance it makes sense to explore how the brain normalises its own biochemistry, using nutrients as the precursors for key neurotransmitters such as serotonin. Thirdly, if 21st century living is extra-stressful, it would be logical to assume that increasing psychological demands would also increase nutritional requirements since the brain is structurally and functionally completely dependent on nutrients.

So, what evidence is there to support suboptimal nutrition as a potential contributor to depression? These are the common imbalances connected to nutrition that are known to worsen your mood and motivation:

- blood sugar imbalances (often associated with excessive sugar and stimulant intake)
- lack of amino acids (tryptophan and tyrosine are precursors of serotonin and noradrenaline)
- lack of B vitamins (vitamin B_6, folate, B_{12})
- lack of essential fats (omega-3).

The sugar blues

One factor that often underlies depression is poor control of blood glucose levels. The symptoms of impaired blood sugar control are many, and include fatigue, irritability, dizziness, insomnia, excessive sweating (especially at night), poor concentration and forgetfulness, excessive thirst, depression and crying spells, digestive disturbances and blurred vision. These symptoms often precede measurable abnormalities in blood glucose, manifesting first as a decreased sensitivity to insulin, known as insulin resistance. One of the world's experts on blood sugar problems, Professor Gerald Reaven from Stanford University in California, USA, estimates that 25% of normal, non-obese people have 'insulin resistance'. Since the brain depends on an even supply of glucose it is no surprise to find that sugar has been implicated in aggressive behaviour,[1–6] anxiety,[7,8] hyperactivity and attention deficit,[9] depression,[10] eating disorders,[11] fatigue,[10] and learning difficulties.[12–15]

The second reason excessive consumption of refined sugar is undesirable is that it uses up the body's vitamins and minerals and provides next to none. Every teaspoon of sugar uses up B vitamins for its catabolism, thereby increasing demand. B vitamins, as we will see, are vital for maintaining mood. About 98% of the chromium present in sugarcane is lost in turning it into sugar. This mineral is vital for keeping the blood sugar level stable.

The amino acid connection

There are often two sides to depression feeling miserable, and feeling apathetic and unmotivated. The most prevalent biochemical theory for the cause of these imbalances is a brain imbalance in two families of neurotransmitters. These are:

- serotonin, thought to primarily influence mood
- dopamine, noradrenaline, and adrenaline, thought to primarily influence motivation.

To test the theory that serotonin primarily controls mood, and adrenaline and noradrenaline control motivation, Antonella Dubini, from the Pharmacia and Upjohn Medical Department in Milan, Italy, gave 203 people suffering from low mood and motivation either a SSRI (selective serotonin reuptake inhibitor) drug, promoting serotonin, or a NARI (noradrenaline reuptake inhibitor) drug, promoting noradrenaline. Sure enough, the former was more effective at improving mood, while the latter was more effective at improving motivation.[16]

Figure 1 shows those nutrients that are required for the production of serotonin, dopamine, adrenaline and noradrenaline.

Depression and tryptophan

SSRI antidepressants are thought to work by stopping the reuptake of serotonin, thereby enhancing serotonin action within the synapse. The trouble is that these kinds of drugs induce unpleasant side effects in as many as a quarter of those who take them, and severe reactions in a minority. An alternative strategy

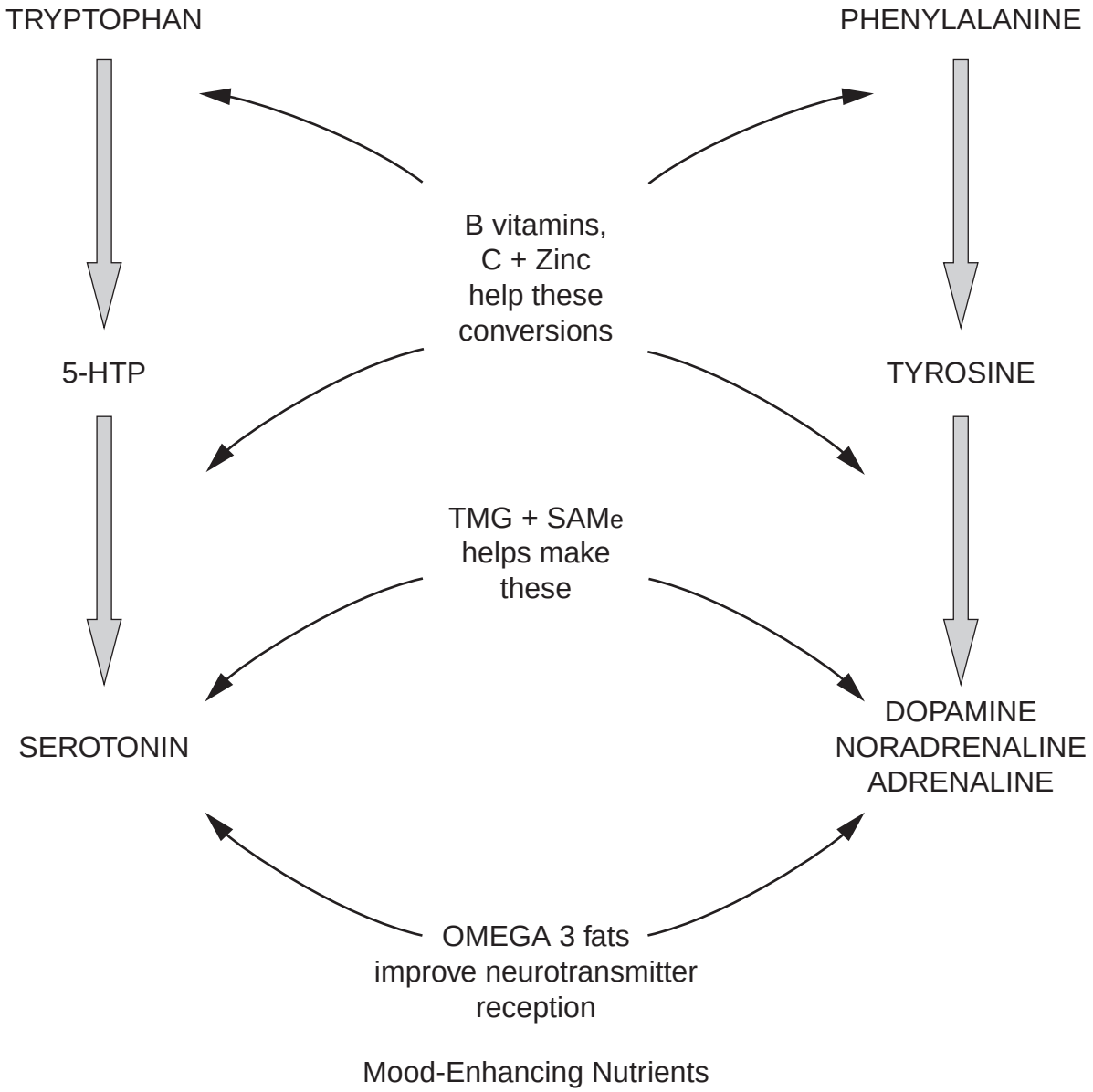

Figure 1 Nutrients that make mood-enhancing neurotransmitters

would be to enhance the synthesis of serotonin by providing optimal amounts of precursor nutrients. But, does it work?

Serotonin is made from the amino acid tryptophan, a constituent of protein. Dr Philip Cowen and colleagues from the University of Oxford, UK, psychiatry department, wondered what would happen if you deprived people of tryptophan. They gave 15 volunteers who had a history of depression, but were currently not depressed, a nutritionally balanced drink that excluded tryptophan. Within seven hours 10 out of 15 noticed a worsening of their mood and started to show signs of depression. On being given the same drink, but this time with tryptophan added, their mood improved.[17] Supplementing the amino acid tryptophan is already proven to improve mood. Donald Ecclestone, professor of medicine at the Royal Victoria Infirmary, Newcastle, UK reviewed the available studies and concluded that supplementing tryptophan is an effective antidepressant, equivalent to tricyclic antidepressants.[18]

While supplementing tryptophan itself has proven a somewhat effective antidepressant, even more effective is a derivative of tryptophan that is one step closer to serotonin. This is called 5-hydroxytryptophan, or 5-HTP for short. The first study proving the mood-boosting power of 5-HTP was done in the 1970s in Japan, under the direction of Professor Isamu Sano of the Osaka University Medical School.[19] He gave 107 patients 50 to 300 mg of 5-HTP per day, and within two weeks, more than half experienced improvements in their symptoms. By the end of the fourth week of the study, nearly three-quarters of the patients reported either complete relief or significant improvement, with no side effects. This study was repeated by Nakajima *et al*. who also found that 69% of patients improved their mood.[20] A trial in Germany found 5-HTP to be as effective as the tricyclic antidepressant imipramine, with a fraction of the side effects.[21] One double-blind trial headed by Dr Poldinger at the Basel University of Psychiatry, Switzerland gave 34 depressed volunteers either the SSRI antidepressant fluvoxamine, or 300 mg of 5-HTP. Each patient was assessed for their degree of depression using the widely accepted Hamilton Rating Scale, plus their own subjective self-assessment. At the end of the six weeks, both groups of patients had had a significant improvement in their depression. However, those taking 5-HTP had a slightly greater improvement in each of the four criteria assessed – depression, anxiety, insomnia and physical symptoms, as well as the patient's self-assessment.[22] Given that 5-HTP is less expensive and has significantly fewer side effects, it is surprising that doctors and psychiatrists virtually never prescribe it.[19,20,23–25]

The recommended dosage of this amino acid, available in any health food shop, is 100 mg of 5-HTP, two or three times a day, for depression. Some supplements also provide various vitamins and minerals such as B_{12} and folic acid, which may be even more effective because these nutrients help to turn 5-HTP into serotonin.

Depression in women

Women are three times as prone to low moods as men. Many theories as to why this is have been proposed, some psychological, some social, but the truth is that women and men are biochemically very different. The research of Mirko Diksic and colleagues at McGill University in Montreal, Canada demonstrates this. They developed a technique using positron emission tomography (PET) neuro-imaging to measure the rate at which we make serotonin in the brain.[26] What they found was that men's average synthesis rate of serotonin was 52% higher than that of women. This, and other research, has clearly shown that women are more prone to low serotonin. They also react differently. In women, low serotonin is associated with depression and anxiety, while in men, low serotonin is related to aggression and alcoholism. One possibility is our social conditioning: men 'act out' their moods, while women are more conditioned to 'act in' their moods.

What has been learnt about serotonin in the last few years is that there are a number of potential reasons for deficiency, in addition to a lack of, or increased need for tryptophan:

- not enough oestrogen (in women)
- not enough testosterone (in men)
- not enough light
- not enough exercise
- too much stress, especially in women
- not enough co-factor vitamins and minerals.

If a person is suffering from low mood, feels tense and irritable, is tired all the time, tends to comfort eat, has sleeping problems and a reduced interest in sex, and some of the above apply, the chances are they are short on serotonin.

Low oestrogen means low serotonin and low moods.[17,27] This is because oestrogen blocks the breakdown of serotonin. This may explain why women are more prone to depression premenstrually and in the menopause and thereafter. Low testosterone has a similar effect in men.

Light also stimulates both oestrogen and serotonin and most of us do not get enough of it. The difference in light exposure outside and inside is massive. Most of us spend 23 out of 24 hours a day indoors, exposed to an average of 100 units (called lux) of light. That is compared to an outdoor level of 20 000 lux on a sunny day and 7000 lux on an overcast day. Now, more than

ever before, many people rarely expose themselves to direct sunlight, and certainly not enough to maximise serotonin production. Of course, light deficiency is worse in the winter.

Stress also rapidly reduces serotonin levels, while physical exercise improves stress response, and therefore reduces stress-induced depletion of serotonin.

Is apathy a catecholamine deficiency?

Another group of neurotransmitters associated with depression and lack of motivation are the catecholamines – dopamine, noradrenaline and adrenaline. As shown in Figure 2, both adrenaline and noradrenaline are synthesised from dopamine, which is made from the amino acid tyrosine, which is itself made from the amino acid phenylalanine. It is logical to assume that, if the drugs that block the breakdown of these neurotransmitters do elevate mood, then augmenting the amino acid phenylalanine or tyrosine might work too. And they do.

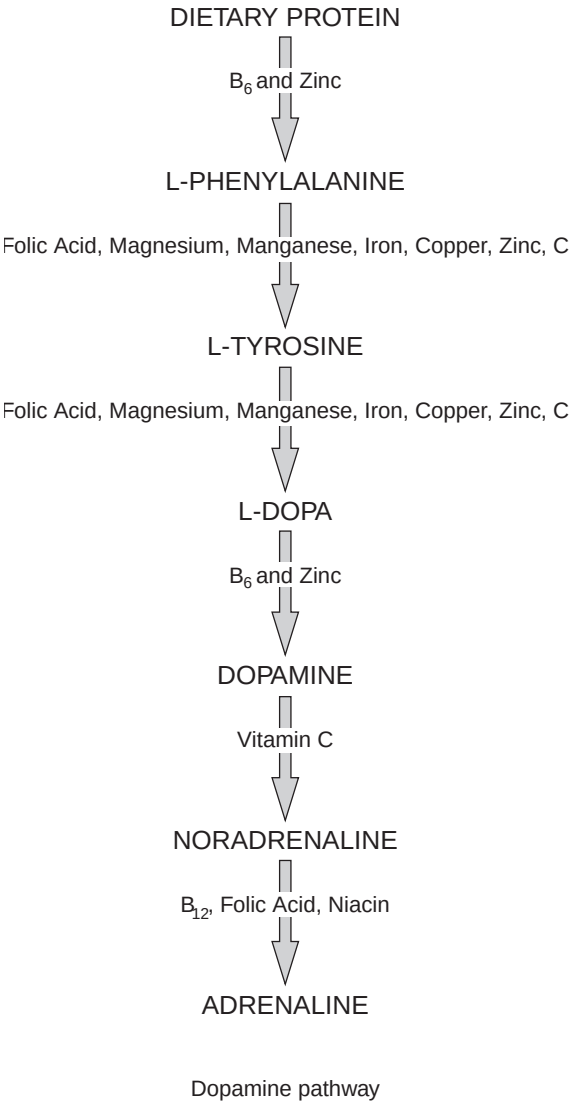

Figure 2 The catecholamine pathway

In a double-blind study by Helmut Beckmann and colleagues at the University of Wurzburg, Germany, 150 to 200 mg of the amino acid phenylalanine, or the antidepressant drug imipramine, were administered to 40 depressed patients for one month. Both groups had the same degree of positive results — less depression, anxiety and sleep disturbance.[28] A group of researchers at the Rush Medical Center, Chicago, USA screened depressed patients by testing phenylethylamine in the blood; low levels mean you need more phenylalanine. They then gave 40 depressed patients supplements of phenylalanine, and 31 of them improved.[29]

Tyrosine has been shown to work well in those with dopamine-dependent depression. In a pilot study administering 3200 mg tyrosine a day to 12 patients at the Hopital du Vinatier, France, a significant improvement in mood and sleep was observed on the very first day.[30]

The military has long known that tyrosine improves mental and physical performance under stress. Recent research from the Netherlands demonstrates how tyrosine gives you the edge in conditions of stress. Twenty-one cadets were put through a demanding one-week military combat training course. Ten cadets were given a drink containing 2 g of tyrosine a day, while the remaining 11 were given an identical drink without the tyrosine. Those on tyrosine consistently performed better, both in memorising the task at hand and in tracking the tasks they had performed.[31]

In our clinical experience the best results are achieved by supplementing all of these amino acids – 5-HTP, phenylalanine and tyrosine – together with the B vitamins that help turn them into neurotransmitters, which are B_6, B_{12} and folic acid.

B vitamins, methylation and depression

B vitamins act as co-factors in key enzymes that control both the production and balance of neurotransmitters. For example, serotonin (5-HT) is produced from 5-HTP by the addition of a methyl group (carboxylase), as is adrenaline from noradrenaline. This enzyme process is highly dependent on folate, as well as vitamins B_{12} and B_6. Folate deficiency is

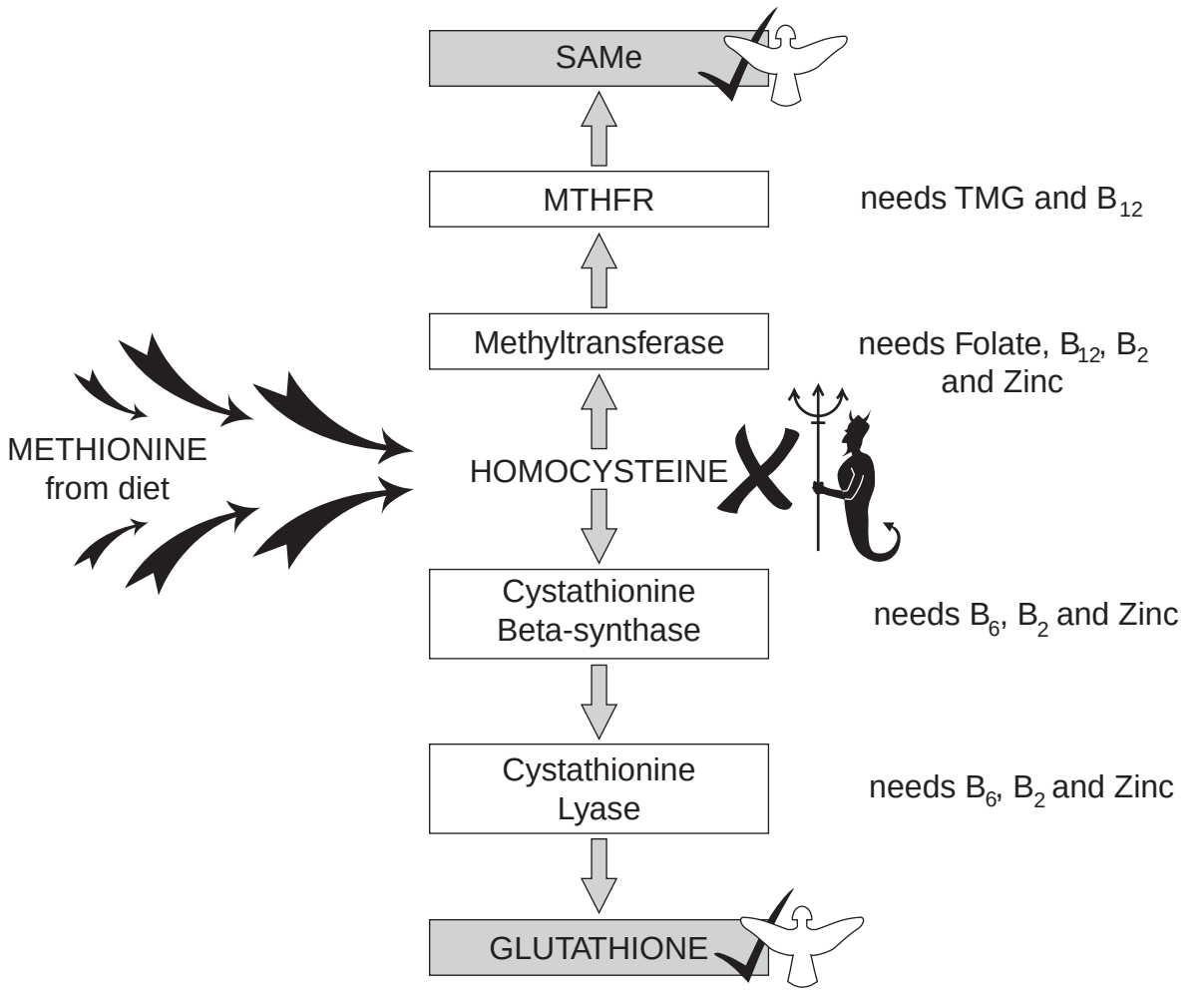

Figure 3 How homocysteine is detoxified

extremely common among depressed patients. In a study of 213 depressed patients at the Depression and Clinical Research Program at Boston Massachusetts General Hospital, USA people with lower folate levels had more 'melancholic' depression and were less likely to improve when given antidepressant drugs.[32] Very depressed people, and also those diagnosed with schizophrenia, are often deficient in folate. A survey of such patients at Kings College Hospital's psychiatry department in London, UK found that one in three had borderline or definite folate deficiency. These patients then took part in a trial where they took folate for six months in addition to their standard drug treatment. Those given folate had significantly improved recovery, and the longer they took the folate, the better they felt.[33]

One current theory is that genetic differences worsening a person's ability to methylate may both increase the tendency to depression (and schizophrenia) and their need for folate, which may be better reflected by measuring homocysteine levels than by measuring blood levels of folate. This is because homocysteine is methylated 'en route' to s-adenosyl methionine (SAMe) by a folate-dependent enzyme methyl-tetrahydrofolatereductase, or MTHFR for short (see Figure 3). In one study, more than half (52%) of patients with severe depression were found to have elevated homocysteine and low levels of folate.[34]

Homocysteine levels are particularly high in patients with schizophrenia, even in the absence of dietary deficiency in folate or vitamin B_{12}.[35] When comparing 193 mixed-sex patients with schizophrenia and 762 non-schizophrenic subjects, US researchers found that average homocysteine levels were a very high 16.3 μmol/l for schizophrenics compared to 10.6 μmol/l in normal subjects.[36] However, the difference between groups was almost entirely attributable to the homocysteine levels of young male patients with schizophrenia.

Genes, homocysteine and mental illness

Not everyone is born equal, as far as methylation is concerned. Around one in ten inherit a defective gene that means that the key methylating enzyme MTHFR does not work so well, increasing the need for folate, as well as vitamins B_{12}, B_6 and zinc. Vitamin B_6 and zinc are involved because those with an MTHFR deficiency accumulate homocysteine, which can also be detoxified by conversion into cystathionine, via an enzyme dependent on pyridoxal-5-phosphate. Pyridoxine (vitamin B_6) is converted to pyridoxal-5-phosphate by a zinc-dependent enzyme. Supplementing a combination of folate, vitamin B_{12} and vitamin B_6 has proven three times more effective at lowering homocysteine than folate alone.[37] The combined efficacy of these nutrients for depression warrants investigation.

While folate deficiency alone can induce depression, the combination of deficiency and a fault in the MTHFR gene is more likely to tip someone over into mental illness. To compensate for this, much higher levels of folate than normal are needed. According to researchers from Columbia University's Department of Psychiatry in New York, USA this also applies to those with schizophrenia. They found increased levels of homocysteine, despite no apparent lack of dietary folate.[38] The same is true for vitamin B_{12}. Many people with mental illness need more than a normal amount of vitamin B_{12} despite no obvious signs of deficiency such as anaemia.[39]

A far better indicator of personal or individualised increased need for these B vitamins is a person's homocysteine level.

SAMe and TMG: the master tuners

In Figures 2 and 3 you might have noticed these two strange-sounding nutrients. Both are kinds of amino acids. TMG stands for tri-methyl-glycine and SAMe stands for s-adenosyl methionine. Unlike the B vitamins discussed above, which act as 'methyl movers', SAMe and TMG are methyl group donors. Both can lower homocysteine levels by donating methyl groups. Conversely, sufficient folate, by enhancing the MTHFR enzyme, can increase production of SAMe.[40] It is a two-way process.

SAMe is one of the most comprehensively studied natural antidepressants. Over 100 placebo-controlled, double-blind studies have shown that SAMe is equal to or superior to antidepressants, works faster, most often within a few days (most pharmaceutical antidepressants may take three to six weeks to take effect) and with few side effects.[41–43] An intake of 200 to 600 mg a day is needed, but the trouble is that it is both very expensive and very unstable. A lot of SAMe sold in health food shops is pretty ineffective. An alternative that is much more stable and less costly is tri-methyl-glycine (TMG). In the body it turns into SAMe, but the supplement needed is three times as much – 600 to 2000 mg a day, on an empty stomach or with fruit.

Mood-boosting fats

Omega-3 fats have a direct influence on serotonin status, probably by enhancing production and reception. According to Dr JR Hibbeln, who discovered that fish eaters are less prone to depression, 'It's like building more serotonin factories, instead of just increasing the efficiency of the serotonin you have'.[44] Dr Basant Puri from London's Hammersmith Hospital, UK reported the case of a 21-year-old student who had been on a variety of antidepressants, to no avail. He had a very low sense of self-esteem, sleeping problems, little appetite, found it hard to socialise and often thought of killing himself. After one month of supplementing ethyle-EPA (eicosapentaenoic acid), a concentrated form of omega-3 fats, he was no longer having suicidal thoughts and after nine months no longer had any depression.[45]

Dr Andrew Stoll and colleagues at Harvard Medical School, USA ran a double-blind placebo-controlled trial of omega-3 fats, placing 14 adult manic depressives on the fish oils EPA and DHA (docosahexaenoic acid) and compared them with 14 taking an olive oil placebo. Both took the supplement alongside their normal medication. Those taking the omega-3 fats had a substantially longer period in remission than the placebo group. The fish oil group also performed better than the placebo group for nearly every other symptom measured.[46] The Institute of Psychiatry in London is currently running a large double-blind trial with fish oils to further evaluate the effects of omega-3 fats on bipolar depression.

Omega-3 fats are effective for severe depression too. A recent trial published in the *American Journal of Psychiatry* tested the effects of giving 20 people suffering from depression, who were already on antidepressants but still depressed, a highly concentrated form of omega-3 fat, ethyl-EPA, versus a placebo. By the third week, the depressed patients were showing major improvement in their mood, while those on placebo were not.[47]

Good mood foods and supplements

There is good logic, and substantial evidence that ensuring optimum nutrition in depressed patients can be highly effective. In addition to simple lifestyle changes such as encouraging exercise and outdoor activity to maximise light, reducing stress and recommending counselling, the following diet and supplement advice may help:

Diet

- Reduce sugar and stimulants (caffeinated drinks and smoking).
- Increase fruit and vegetables (five servings a day).
- Eat oily fish (mackerel, tuna, salmon, herring) at least twice a week.
- Ensure sufficient protein from fish, meat, eggs, beans and lentils.

Supplements

- B complex, including vitamin B_6 10 mg, folate 400 μg and vitamin B_{12} 10 μg.
- Additional folate, 400 to 2000 μg a day.
- 5-HTP 200–300 mg a day.
- Omega-3-rich fish oil, two capsules a day, giving at least 400 mg of EPA.

ACKNOWLEDGEMENTS

This article has been adapted from Patrick Holford's new book *Optimum Nutrition for the Mind* (Piatkus, £16.99). For further information call +44 (0)20 8871 2949 or visit www.mentalhealthproject.com.

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