

# Treatment of depression: time to consider folic acid and vitamin B<sub>12</sub>

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## Abstract

We review the findings in major depression of a low plasma and particularly red cell folate, but also of low vitamin B<sub>12</sub> status. Both low folate and low vitamin B<sub>12</sub> status have been found in studies of depressive patients, and an association between depression and low levels of the two vitamins is found in studies of the general population. Low plasma or serum folate has also been found in patients with recurrent mood disorders treated by lithium. A link between depression and low folate has similarly been found in patients with alcoholism. It is interesting to note that Hong Kong and Taiwan populations with traditional Chinese diets (rich in folate), including patients with major depression, have high serum folate concentrations. However, these countries have very low life time rates of major depression. Low folate levels are furthermore linked to a poor response to antidepressants, and treatment with folic acid is shown to improve response to antidepressants. A recent study also suggests that high vitamin B<sub>12</sub> status may be associated with better treatment outcome. Folate and vitamin B<sub>12</sub> are major determinants of one-carbon metabolism, in which S-adenosylmethionine (SAM) is formed. SAM donates methyl groups that

are crucial for neurological function. Increased plasma homocysteine is a functional marker of both folate and vitamin B<sub>12</sub> deficiency. Increased homocysteine levels are found in depressive patients. In a large population study from Norway increased plasma homocysteine was associated with increased risk of depression but not anxiety. There is now substantial evidence of a common decrease in serum/red blood cell folate, serum vitamin B<sub>12</sub> and an increase in plasma homocysteine in depression. Furthermore, the MTHFR C677T polymorphism that impairs the homocysteine metabolism is shown to be overrepresented among depressive patients, which strengthens the association. On the basis of current data, we suggest that oral doses of both folic acid (800 µg daily) and vitamin B<sub>12</sub> (1 mg daily) should be tried to improve treatment outcome in depression.

## Keywords

cobalamin, depression, diet, folate, folic acid, homocysteine, one carbon-metabolism, S-adenosylmethionine, vitamin B<sub>12</sub>

## Introduction

The WHO ranks unipolar depression as the fourth most important cause of mortality and disability (Murray and Lopez, 1997). Depression has an overall prevalence of 5–8%. The prevalence of late life depression is estimated to be 15%, but there is a great under-diagnosis and under-treatment of late life depression. Persons with neurodegenerative disorders are at high risk of depression. In Alzheimer's disease, the frequency of depression is around 50% (Gottfries, 2001). The risk of suicide is calculated to be 20 times of that of a general population, and between 50% and 70% of all people who commit suicide suffer from depressive illness (Barraclough *et al.*, 1974; Isacson, 2000).

Although many new antidepressant drugs have been introduced recently, response rates have not improved and the treatment of depressive illness remains unsatisfactory. The selective serotonin

reuptake inhibitors, as well as the older tricyclic antidepressants, have a response rate of approximately 50%, compared to 32% on placebo (Agency for Health Care Policy and Research, 1999; Gottfries, 2001). Depressive illness is a periodic illness; the length of the period of each episode can vary widely. The illness is also recurrent such that the lifetime morbidity can be considerable (Angst *et al.*, 2003).

Most consensus statements suggest continuation of treatment for 4–9 months after recovery and long-term maintenance treatment after three or more episodes (Geddes *et al.*, 2003). It should be remembered that only 50% of patients respond in the first place. The response to electroconvulsive therapy (ECT) is significantly better than antidepressants because 78% of patients respond to this treatment (Janicak *et al.*, 1985). Even so, continuation treatment with antidepressants or lithium is essential after ECT to prevent relapses (Coppen *et al.*, 1981; Abou-Saleh and Coppen, 1988).

Little is known about age-related or exogenous factors that may contribute to depression. However, there is increasing evidence that a disturbed one-carbon metabolism, of which an elevated homocysteine level is a marker, may be a significant factor contributing to depressive disorders. During the Fourth International Homocysteine Conference in 2003 (Basel), there was a noticeable increase in the number of presentations focusing on psychiatric disorders. Nevertheless, the awareness of this connection is not widespread and it may be useful to highlight the evidence that supports the importance of folate and vitamin B<sub>12</sub> status in depression.

### Low folate levels are common in depressive patients

Folate status is an important determinant of plasma homocysteine; low serum and/or red blood cell (RBC) folate is linked with high plasma homocysteine, as shown in a very large number of studies (Homocysteine Lowering Trialists' Collaboration, 1998).

Low folate levels have been found in many studies of depressive patients. Shorvon *et al.* (1980) reported that no less than 56% of patients with affective disorders had folate deficiency. Abou-Saleh and Coppen (1986, 1989) found significantly lower serum and RBC folate in patients with major depressive disorder compared to healthy controls. Lower serum folate concentrations were also associated with greater severity of depression. Carney *et al.* (1990) found that RBC folate was significantly lower in depressive

patients compared to patients with other psychiatric diagnoses. Several other studies have demonstrated low or low normal serum or RBC folate in 15–38% of depressive patients. Associations between disease severity and duration with folate status are also found. A recent study by Morris *et al.* (2003) found low folate status in depressed members of a general US population sample aged 15–39 years. After adjustment for relevant factors, subjects with a lifetime diagnosis of major depression had folate concentrations in serum and RBC that were lower than never-depressed subjects. Subjects with dysthymia alone had lower RBC-levels of folate than never-depressed, but serum levels did not differ. Low folate status was found to be most characteristic of recently recovered subjects. The authors conclude that folate supplementation may be indicated during the year following a depressive period.

In patients with chronic and recurrent mood disorders treated by lithium, Coppen and Abou-Saleh (1982) found that patients with higher plasma folate (> 18.12 nmol/l or > 8.0 ng/ml) had very significantly lower affective morbidity over 2 years compared to patients with decreased folate levels. In a subsequent trial at the same clinic, the addition of a small daily supplement of folic acid (200 µg) was found to significantly reduce morbidity in patients whose plasma folate was increased to 13 nmol/l (5.74 ng/ml) or above (Coppen *et al.*, 1986).

There is also evidence that folate is involved with the depression of chronic alcoholism (Merry *et al.*, 1982). Eighteen out of 41 patients, who had a plasma folate of 15.9 nmol/l (7 ng/ml) or more, had a mean Beck depression score of  $10.8 \pm 1.9$  compared to 23 patients with lower plasma folate levels, whose mean depression

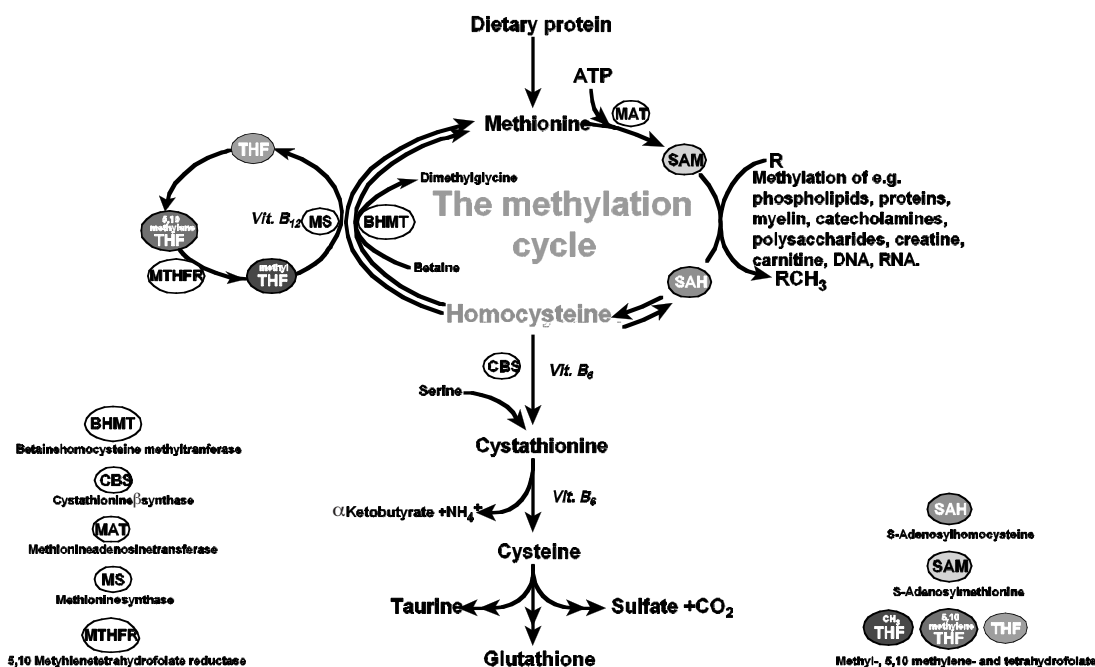


Figure 1 Homocysteine metabolism

score was  $21.0 \pm 2.2$  ( $p < 0.001$ ). The role of folic acid in depression is reviewed by Abou-Saleh and Coppen (1986) and by Alpert *et al.* (2000).

Depressive symptoms also considerably contribute to morbidity in various neurological diseases, such as Parkinson's disease and epilepsy, which are both associated with low folate status. Levodopa increases the requirement of S-adenosylmethionine (SAM) for its turnover. SAM requires folate and vitamin B<sub>12</sub> for its synthesis (Fig. 1). Antiepileptics also affect the one-carbon metabolism mainly by impairing folate status; low folate levels and depression and other mental changes are common in epileptics (Edeh and Toone, 1985; Rosche *et al.*, 2003). Depression also often accompanies ageing and dementia, which are associated with both folate and B<sub>12</sub> deficiency. These associations were recently reviewed by Reynolds (2002). As discussed below, low levels of folate in depression have important implications for plasma homocysteine.

An interesting study from Hong Kong found that patients with major depression had normal serum folate levels (Lee *et al.*, 1998). In this area, the traditional Chinese diet contains a high proportion of green vegetables and is hence rich in folate (Lee *et al.* 1992). Nevertheless, the study also showed that patients who responded well to lithium maintenance treatment had higher serum folate concentrations than those with unsatisfactory response ( $p < 0.05$ ). It should also be noted that the rate of lifetime major depression is much lower in some countries with Chinese diets (e.g. 1.5% in Taiwan) than in Europe (e.g. 16.4% in France) (Chen *et al.*, 1993; Weissman *et al.*, 1996).

Finally, low plasma folate and raised homocysteine have been linked to heart disease and strokes in a very large number of studies. There is also a link between depression, heart disease and increased risk of dying after a cardiac infarction (Glassman and Shapiro, 1998). These connections provide a plausible reason for these two groups of serious disease to be connected. An extensive review on determinants for homocysteine concentrations and the evidence to what extent hyperhomocysteinemia determines the risk of vascular disease was recently published (De Bree *et al.*, 2002).

## Vitamin B<sub>12</sub> levels are also often low in depression

Carney and Sheffield (1978) found that up to 31% of depressive patients had low vitamin B<sub>12</sub> serum levels. However, only a fairly small proportion (5–20%) of total serum cobalamin is bound to transcobalamin (holotranscobalamin) in serum and is thus available for transport to metabolically active cells. Total serum B<sub>12</sub> is therefore a relatively poor indicator of B<sub>12</sub> activity, as several factors may alter the binding to transcobalamin and therefore its distribution (McCaddon *et al.*, 2002). More recent studies have also used homocysteine and/or methylmalonic acid as functional markers of vitamin B<sub>12</sub> deficiency. The American Women's Health and Ageing Study (Penninx *et al.*, 2000) reported functional vitamin B<sub>12</sub> deficiency to be commoner among depressive than among non-depressive elderly women. Metabolically significant vitamin

B<sub>12</sub> deficiency was present in 17% of mildly depressed subjects and in 27% of severely depressed subjects in this community-based study. Subjects with vitamin B<sub>12</sub> deficiency (serum levels  $< 148$  pmol/l or 200 pg/ml) were more than twice as likely as non-deficient subjects to be depressed after adjustment for other relevant factors. In this study, there were no significant differences in serum folate or homocysteine levels between groups (Penninx *et al.*, 2000).

Another recently published population-based study of elderly subjects, the Rotterdam study, showed that hyperhomocysteinemia ( $> 13.9$   $\mu$ mol/l), vitamin B<sub>12</sub> deficiency (serum levels  $< 258$  pmol/l or 350 pg/ml) and, to a lesser extent, folate deficiency (serum levels  $< 11.4$  nmol/l or 5.0 ng/ml) was significantly related to depressive disorders (DSM-IV criteria). However, after adjustment for other relevant factors, the association with hyperhomocysteinemia and folate deficiency was substantially reduced, whereas the association with vitamin B<sub>12</sub> deficiency appeared to be independent. Subjects with vitamin B<sub>12</sub> deficiency were 70% more likely to have severe depressive disorder than subjects without deficiency (Tiemeier *et al.*, 2002).

There are limitations in these studies. It is conceivable that depression may alter nutrition and vitamin intake. Correction for confounding factors and interpretation may be difficult. A recent Finnish study reported current vitamin intake in a cross-sectional general population of 2682 men aged 42–60 years, where there were 228 men with current depressive symptoms. Subjects with previous history of psychiatric disorder were excluded. Subjects in the lowest third of energy-adjusted folate intake had a 67% greater risk of being depressed than those in the highest third, and the difference remained significant after adjustment for possible confounding factors (Tolmunen *et al.*, 2003). The same authors later determined RBC folate and serum B<sub>12</sub> levels in 115 outpatients with DSM-III-R major depressive disorder at baseline and after 6 months of antidepressive treatment. Higher vitamin B<sub>12</sub> status was associated with better treatment outcome, whereas the association with folate status was weaker (Hintikka *et al.*, 2003).

## One-carbon metabolism

Homocysteine is an intermediate product in the one-carbon metabolism and is formed during the metabolism of methionine in the methylation cycle (Fig. 1). Three enzymes are directly involved in this metabolism: methionine synthase (MS), betaine homocysteine methyltransferase, and cystathionine  $\beta$ -synthase (CBS). The MS-mediated recycling of homocysteine is indirectly regulated by methylenetetrahydrofolate reductase (MTHFR).

Dietary methionine is either used for protein synthesis, or formation of SAM, which contains a reactive methyl group. This is easily transferred to a large variety of acceptor substrates, including nucleic acids, proteins, phospholipids, myelin, polysaccharides, choline, catecholamines and a large number of small molecules. The majority of tissues, including the central nervous system, are entirely dependent on methyl groups derived from the MS-mediated recycling of homocysteine. When SAM is

demethylated, S-adenosylhomocysteine (SAH) is formed. SAH is a potent methylation inhibitor by competing with SAM at binding sites. SAH is hydrolysed in a reversible reaction to homocysteine, which can be recycled to methionine and SAM, or be directed towards the transsulphuration pathway. Vitamin B<sub>12</sub> is cofactor to MS, and vitamin B<sub>6</sub> to CBS. Methyl tetrahydrofolate (methylTHF) is substrate in the MS-mediated recycling of homocysteine. This reaction is also critical for the formation of active folate forms, which are required for purine and thymidine synthesis, and thus for DNA synthesis and repair.

MTHFR mediates the formation of methylTHF, and therefore has a strong, indirect influence on the remethylation of homocysteine. A rapidly increasing number of variations (some of them quite common) of the genes regulating this and other enzymes involved in the one carbon metabolism are being identified. Approximately 200 references are published on just one polymorphism of the MTHFR gene (677C>T). It results in a thermolabile form and reduced enzyme activity. The TT genotype is associated with a mean increase of homocysteine levels by approximately 25%. However, the impact is dependent on folate status. This may explain why the T allele is over-represented in some, but not in all, studies of conditions associated with elevated homocysteine levels. This C677T polymorphism is present in its homozygous form in approximately 10% of white US, and most European, populations, but the frequency varies substantially geographically and with ethnicity. An overview of this biochemical system is given in a recent monograph focusing the association with neuropsychiatric conditions (Bolander-Gouaille and Bottiglieri, 2003).

### Factors contributing to increased homocysteine levels

In addition to reduced plasma folate levels and B<sub>12</sub>, there is often a cluster of underlying factors that can increase plasma homocysteine levels. These include smoking and high alcohol intake, which impair vitamin status, and low intake or malabsorption of vitamins, common defects of the MTHFR gene, diseases and drug interactions. An additive effect of lifestyle factors, vitamin malabsorption owing to common atrophic gastritis, and other declining physiological, age-related changes, may explain the age-associated increase of homocysteine. Furthermore, many drugs interact, either by reducing the absorption of cofactors (e.g. anti-ulcer agents and biguanides) or by increasing the catabolism/requirement of the vitamins, such as antiepileptics and levodopa. Autoimmune diseases such as hypothyroidism, rheumatoid arthritis, systemic lupus erythematosus and diabetes, are also associated with elevated homocysteine levels. A recent review has addressed these and other aspects of homocysteine determination (Refsum *et al.*, 2004).

### Biochemical mechanisms related to the one-carbon metabolism may influence brain function in depression

Increased homocysteine points toward decreased recycling of homocysteine to SAM, as well as increased SAH levels, resulting in decreased methylation capacity that may impair synthesis of neurotransmitters and membrane phospholipids. Another biochemical explanation for the association between a disturbed one-carbon metabolism and depression is reduced availability of tetrahydrobiopterin (BH<sub>4</sub>), which is dependent on folate for its turnover (Coppen *et al.*, 1989; Bottiglieri *et al.*, 1992). This compound is a potent endogenous antioxidant. It is also a cofactor for the hydroxylation of tyrosine and tryptophan required for the synthesis of dopamine and serotonin. It is also suggested to interact with nitric oxide, an apparent neuroendocrine modulator of the hypothalamic-pituitary-adrenal axis, which may be involved in the pathogenesis of depression (van Amsterdam and Oppenhuizen, 1999). Finally, homocysteine may cause vascular injury by several oxidative mechanisms and thereby contribute to cerebral dysfunction.

Decreased brain 5-HT synthesis was previously demonstrated in folate deficiency (Botez *et al.*, 1979). An association was later found between low cerebrospinal fluid (CSF) levels of 5-HIAA and both vitamin B<sub>12</sub> and folate deficiency in patients with neuropsychiatric symptoms, including depression. 5-HIAA returned to normal with folate treatment in patients with folate-responsive neuropsychiatric symptoms (Botez *et al.*, 1982). Severely depressed patients with homocysteine levels > 12 µmol/l (52% of sample) were later found to have lower CSF levels of 5-hydroxyindoleacetic acid, homovanillic acid, and 3-methoxy-4-hydroxy-phenylethylene glycol compared to patients with lower homocysteine levels, which indicates disturbances in serotonin, dopamine and noradrenaline turnover. Homocysteine and folate concentrations were correlated, and nearly one-third of these severely depressed patients had RBC folate concentrations 340 nmol/(150 ng/ml). Furthermore, low CSF SAM levels, confirming reduced methylation capacity, accompanied high homocysteine levels (Bottiglieri *et al.*, 2000).

### Association between MTHFR 677C>T polymorphism now strengthens the evidence that altered one-carbon metabolism predisposes for depression

An association with genetic factors that impair the homocysteine metabolism would strengthen the association with depression. Increased postprandial levels of homocysteine, but normal fasting levels in depressive patients, were proposed to indicate some enzymatic defect (Candito *et al.*, 1997) (i.e. a large methionine load stresses the metabolism). In the same year, a study of the prevalence of the C677T polymorphism in patients with major depression showed that the TT genotype was more than twice as common in patients compared to controls (Arinami *et al.*, 1997). Patients with late-onset depression were later found to have a frequency of

the T allele of 74% versus 48% for early onset depression (Hickie *et al.*, 2001). However, other studies found no association, but these studies were small and folate status was generally not taken into account.

A large population-based study now strongly supports the association. Anxiety and depression were measured by the Hospital Anxiety and Depression Scale in 5948 subjects aged 46–49 years and 70–74 years in the Norwegian Hordaland study. Plasma homocysteine levels  $\geq 15 \mu\text{mol/l}$  were found to be associated with an increased risk of depression. Furthermore, the 677 TT genotype of the MTHFR gene was similarly associated with a 69% increased risk. Low plasma folate, which is considered to be less reliable than RBC folate, was significantly related to depression only in a subgroup of middle-aged women; vitamin B<sub>12</sub> levels  $< 230 \text{ pmol/l}$  (312 pg/ml) were associated with high depression scores (Bjelland *et al.*, 2003).

### Impact of vitamin status for treatment outcome

A study of 101 depressed inpatients treated with different antidepressive drugs by Reynolds *et al.* (1970) showed that the therapeutic effect was inferior if serum folate was low. More recently, a study of severely depressed outpatients showed that the patients, who responded to treatment with desmethylimipramine, had significantly better folate status than non-responders. There was also an inverse association between RBC folate and severity of depression and age at disease appearance. In addition, B<sub>12</sub> status was better in responders (Wesson *et al.*, 1994). Another study showed that therapy resistance to fluoxetine was significantly increased in patients with low serum folate (Fava *et al.*, 1997).

A recent report indicates that the therapeutic effect of both a selective serotonin reuptake inhibitor (SSRI) (sertraline) and a tricyclic antidepressant (nortriptyline) is dependent on baseline RBC folate, even though all folate levels were in the normal range. Higher folate status in geriatric depression predicted better outcome and the association was strongest for sertraline (Alpert *et al.*, 2003). Interestingly, antidepressant therapy is shown to be accompanied by an increase of RBC folate, which is dependent on both folate and vitamin B<sub>12</sub> status, and the increase was greater in responders than in non-responders (Levitt *et al.*, 1998).

The synthesis of the essential methyl group donor SAM is folate and vitamin B<sub>12</sub> dependent. SAM is used for the treatment of depression in some countries, either alone or in combination with antidepressants. The effect has been estimated to be comparable with the effect of tricyclic antidepressants, but better tolerated and with a faster onset of action (Mischoulon and Fava, 2002; Pancheri *et al.*, 2002). SAM was also recently found to be effective in depression related to Parkinson's disease (Di Rocco *et al.*, 2000). A review of the literature on SAM and depression is provided by Papakostas *et al.* (2003).

### The effect of homocysteine-lowering vitamin supplementation in depression

Folic acid alone may have an antidepressant effect. A placebo-controlled study of severely depressed patients with RBC folate  $< 453 \text{ nmol/l}$  ( $< 200 \text{ ng/ml}$ ) showed better symptom relief and social adaptation in those treated by 15 mg of folic acid/daily compared to placebo (Godfrey *et al.*, 1990). Another double-blind study showed comparable effects by 50 mg of folic acid and by 100 mg/daily of trazodone in elderly depressed and demented patients. In this study, the folate RBC levels were within the reference limits (Passeri *et al.*, 1993).

A placebo-controlled double-blind study of 41 patients with major acute depression or schizophrenia and with RBC folate  $< 453 \text{ nmol/l}$  ( $< 200 \text{ ng/ml}$ ) showed that daily supplementation with 15 mg of methylfolate for 6 months, in addition to standard psychotropic treatment, enhanced the therapeutic effect in both diagnoses; the effect also increased with time (Procter, 1991).

A placebo-controlled study in patients with major depression showed that 0.5 mg of folic acid daily, in addition to 20 mg of fluoxetine, resulted in a decrease of more than 50% in Hamilton rating scale scores in 93.3% of female depressive patients. This was significantly better than the 61.1% in the placebo group. The homocysteine level decreased significantly in the folic acid group only in women. In men, there was no significant difference in homocysteine levels during treatment and no significant difference in therapeutic response between men receiving folic acid or placebo. This was most likely the result of too low a dose of folic acid (Coppen and Bailey, 2000). A recent 8-week open study also indicated that 15–30 mg daily of folic acid enhanced the effect in SSRI-refractory depression (Alpert *et al.*, 2002).

A recent Cochrane review, based on three intervention trials, including 247 patients, concludes that folate may have a potential role as a supplement to other treatment for depression, although it is not clear if this is the case both for patients with normal and low folate levels (Taylor *et al.*, 2004).

It is urgent that larger double-blind randomized intervention studies are performed to determine to what extent homocysteine-lowering vitamins and other measures aiming to optimize one-carbon metabolism can improve management of depression. These studies should include measurements of functional markers of vitamin status, such as homocysteine, that reflect the functional interaction between the vitamins and enzymes.

### Implications for management of depression

There is now substantial evidence of a decrease in plasma folic acid and vitamin B<sub>12</sub> and an increase in plasma homocysteine in depressive patients. In spite of the absence of large-scale systematic studies of vitamin supplementation on the course of the illness, we suggest there is a good case for starting vitamin supplements in patients with depression. However, we should stress that these recommendations are provisional and await additional evidence obtained from large systematic trials.



A daily oral dose of 800 µg of folic acid is calculated to be adequate in most cases (Wald *et al.*, 2001). The required dose of vitamin B<sub>12</sub> depends on how depleted the patient's stores are, and on the underlying reason for a deficiency. For maintenance therapy, a daily oral dose of 1 mg (of which approximately 1% is absorbed by diffusion, independently of intrinsic factor) is generally considered adequate. Caution should be used in patients with megaloblastic anaemia, which can be caused both by folate and B<sub>12</sub> deficiency. Folic acid supplementation may mask anaemia caused by B<sub>12</sub> deficiency, whereas other symptoms may progress.

If further investigations confirm these links between depression and vitamin supplementation, we should be able both to improve the response to treatment and also reduce relapses, which comprise a distressing aspect of this illness.

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