Depressão e Ácido Fólico

Folate for depressive disorders
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A substantive amendment to this systematic review was last made on 22 February 2003. Cochrane reviews are regularly checked and updated if necessary.

Abstract

Background
There are a number of effective interventions for the treatment of depression. It is possible that the efficacy of these treatments will be improved further by the use of adjunctive therapies such as folate.

Objective
1. To determine the effectiveness of folate in the treatment of depression
2. To determine the adverse effects and acceptability of treatment with folate.

Search strategy
The Cochrane CENTRAL Register of Controlled Trials (CENTRAL), and the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Registers (CCDANCTR-Studies and CCDANCTR-References - carried out on 12/5/2005) were searched. Reference lists of relevant papers and major textbooks of affective disorders were checked. Experts in the field and pharmaceutical companies were contacted regarding unpublished material.

Selection criteria
All randomised controlled trials that compared treatment with folic acid or 5'-methyltetrahydrofolinic acid to an alternative treatment, whether another antidepressant medication or placebo, for patients with a diagnosis of depressive disorder (diagnosed according to explicit criteria).

Data collection and analysis
Data were independently extracted from the original reports by two reviewers. Statistical analysis was conducted using Review Manager version 4.1.

Main results
Three trials involving 247 people were included. Two studies involving 151 people assessed the use of folate in addition to other treatment, and found that folate reduced Hamilton Depression Rating Scale scores on average by a further 2.65 points (95% confidence interval 4 to 33). One study involving 96 people assessed the use of folate instead of the antidepressant trazodone and did not find a significant benefit from the use of folate. The trials identified did not find evidence of any problems with the acceptability or safety of folate.

Reviewers' conclusions
The limited available evidence suggests folate may have a potential role as a supplement to other treatment for depression. It is currently unclear if this is the case both for people with normal folate levels, and for those with folate deficiency.

Synopsis
This systematic review was undertaken to see if giving folate to people with depressive disorders reduced their depressive symptoms. Three randomized trials were identified, involving a total of 247 people. In all three trials, folate was well tolerated. In two of these trials, folate was added to other antidepressant drug treatment and there was limited evidence that folate helped. In the third trial, folate was compared to trazodone, an antidepressant drug. No difference was found. There is therefore limited evidence that adding folate to other antidepressant may be helpful, but larger trials are needed before patients and clinicians can be confident that it will be helpful.

Background
Depression is a major cause of worldwide disability. In the United States the one month prevalence of a major depressive episode has been estimated to be 2.2% (Regier 1988) and comparable figures have been found in the U.K. (Jenkins 1997). The Global Burden of Disease Study found unipolar depression to be the fourth leading cause of worldwide disability even after excluding deaths due to suicide (Murray 1997a). The prevalence of major depressive disorder may be on the increase (CNCG 1992) and the Global Burden of Disease Study predicted that, by 2020, unipolar major depression will be the second leading cause of disability worldwide (Murray 1997b). There is therefore limited evidence that adding folate to other antidepressant may be helpful, but larger trials are needed before patients and clinicians can be confident that it will be helpful.

Folate levels have been linked to a worse response to pharmacological treatment (Geddes 2001). Since the introduction of antidepressants in the 1950s, the number of available pharmacological treatments has increased, but their efficacy has remained largely unchanged. A recent review reported a response rate of 50% with active drug compared to 32% with placebo (AHCPR 1999). One possible method of improving response to antidepressant medication is by using adjunctive agents such as amino acid precursors and cofactors. One such agent is folic acid, which is the parent compound of a number of naturally occurring folates. Dietary folates are absorbed and carried in the blood in the form of 5'-methyltetrahydrofolate. Within the body, folates act as important methyl donors in the reactions of DNA synthesis and amino acid metabolism. Folate deficiency is a common finding in psychiatric patients, whether measured by serum folate (Carney 1967, Reynolds 1970, Reynolds 1976) or red blood cell folate (Reynolds 1971, Carney 1990). While low levels have not been found in all populations (Lee 1992, Lee 1998), lower folate levels have been linked to a worse response to pharmacological treatment (Fava 1997). An association between folate and serotonin metabolism has been demonstrated in patients with neuropsychiatric disorders (Botez 1990).
1982) and patients with inborn errors of folate metabolism (Clayton 1986, Hyland 1988). The basis of this link may be the role played by folate in the methylation of homocysteine, which is necessary for its conversion to s-adenosylmethionine (SAM), since SAM has itself been shown to influence serotonin metabolism (Bottigeri 1984), and has been used in the treatment of depression (Agnoi 1976, Caruso 1984). Alternatively, it has also been shown that folates also play a role in the methylation reactions producing tetrahydrobiopterin (Kauffman 1991), which is an essential co-factor for the hydroxylase enzymes which form the rate-limiting step in the production of monoamines including serotonin (Kauffman 1981). There is some evidence of gender differences in tetrahydrobiopterin metabolism (Coppen 1989).

Dietary folate supplementation has appeared effective and reasonably tolerated in other contexts such as the treatment of the megaloblastic anaemia of folate deficiency, or the prevention of neural tube defects (MRC VSRG 1991, Creizel 1992). This review aims to assess whether treatment with folate, either alone or as an adjunct to other antidepressant medication, is effective in the treatment of depression.

### Description of studies

Three randomised controlled trials satisfied the inclusion criteria for this review.

**Participants**

Two trials (151 patients randomised) were conducted in patients over the age of 18 (Coppen 2000, Godfrey 1990). Both required a DSM-III or DSM-III-R diagnosis of major depression and in addition, a score of 20 or more on the HDRS was required to be included in the Coppen study. A low folate level (less than 200 µg/litre) was necessary for inclusion in the study by Godfrey. However, abnormal laboratory tests (including megaloblastic anaemia), were an exclusion criterion in the Coppen study.

The third trial (Passeri 1991) included 96 patients who were all aged at least 65. Only patients with a DSM diagnosis of dementia, MMSE of 12-23, and depression with a Hamilton Depression Rating Scale score of greater than 18 were included. All participants had red blood cell folate in the normal range. In this trial patients who responded to a two week placebo run-in period were excluded.

Setting

All three trials were conducted in Europe, two in the UK (Coppen 2000, Godfrey 1990) and one in Italy (Passeri 1991). Godfrey et al recruited both outpatients and inpatients while in the Coppen trial the sample was selected predominantly from outpatients. The study in older adults with comorbid depression and dementia was conducted in a nursing home.

Interventions used

Two studies compared treatment with folate to placebo in the context of continued use of other psychotropic medication. Of these, one used 500µg folic acid (Coppen 2000), and the other 15mg methyltetrahydrofolate (Godfrey 1990). One trial compared the use of 50mg methyltetrahydrofolate once daily to 50mg trazodone twice daily (Passeri 1991).

Duration of follow-up

The durations in the trial of the studies were eight weeks (Passeri 1991), ten weeks (Coppen 2000) and six months (Godfrey 1990).

Outcome measures

All studies used a Hamilton Depression Rating Scale (either 17 or 21 item) to measure depressive symptoms. Information on drop-out rates was also included. Two studies reported the number of subjects reporting adverse event (Coppen 2000, Passeri 1991), and one reported admissions to hospital (Coppen 2000). One study (Godfrey 1990) reported a clinical outcome scale combining clinician impressions of improvement in both symptoms and social functioning.

### Results

Resolution of a depressive episode

Continuous rating scales (Hamilton Depression Rating Scale (HDRS)) were used in all studies allowing comparison of scores between different treatment groups after defined periods.

Pooling the results of the two trials that compared folate with placebo in addition to other psychotropic medication, the weighted mean difference (WMD) in HDRS score between the groups at trial end point favoured treatment with folate, (WMD -2.65; 95% CI -4.93 to -0.38; heterogeneity chi-square=0.01, p = 0.91). Although this result is statistically significant, the confidence interval is wide. When difference (WMD) in HDRS score between the groups at trial end point favoured treatment with folate, (WMD -0.90; 95% CI -1.45 to -0.35).

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When compared to trazodone (Coppen 2000), or trazodone, RR 0.97 (95% CI 0.95 to 1.05) (Coppen 1990), published separate data for male and female subjects. There was no statistically significant difference in HDRS score for male subjects treated with either folate or placebo, WMD 1.20 (95% CI -3.61 to 6.01). In contrast, HDRS score for female subjects was improved with folate, WMD -4.60 (95% CI -7.40 to -1.80). Although the 95% CIs of male and female subjects overlap, there was statistically significant heterogeneity between the two groups on this measure (chi-square=4.18, p=0.041).

Similarly, considering the outcome of less than 50% reduction in HDRS, in the male subgroup there was no difference between folate and placebo, RR 1.07 (95% CI 0.48 to 2.38), while for the female group results favoured folate, RR 0.16 (95% CI 0.04 to 0.63); there was also statistically significant heterogeneity on this outcome (chi-square=6.36, p=0.012). If data regarding the relationship between treatment response and gender becomes available from the authors of other studies, it will be included in subsequent versions of this review.

Dysthymia versus Other Diagnosis

No trials were identified assessing the efficacy of folate in dysthymia, so this subgroup analysis could not be performed.
Sensitivity Analyses
Due to the small number of included trials, no sensitivity analyses were performed.

Discussion
Use of folate as augmentation
There is some evidence that augmentation of antidepressant treatment with folate may improve outcome. The existence of one or two relatively small - or negative - trials would have a substantial effect on the pooled estimate. As there are few studies, indirect methods of identifying publication bias such as funnel plots are of very limited value. The limited evidence also limits the precision of the results - this means that the size of any potential benefit is uncertain, and may be clinically insignificant. When the results are expressed as a continuous variable, the difference in Hamilton Depression scale score lies between 0.4 and 4.9. Similarly the NNT for dichotomous outcomes may be as few as 4 or as many as 97.

Use as alternative to other antidepressant
Only one trial was identified that examined the use of folate as an alternative to conventional antidepressant therapy (Passeri 1991) and this identified no clear benefit from the use of folate. However, it was underpowered to measure a moderate treatment difference between folate and trazodone. The dosage of trazodone used was relatively low, and it was in a group of patients with comorbidity dementia, which may limit generalisability.

Acceptability/adverse events
The included trials did not find evidence that the use of folate supplementation or folate compared to trazodone was associated with any statistically significant problems of acceptability or adverse events. However, small total number of patients randomised mean that infrequent but serious adverse events cannot be excluded.

Subgroup effects
There is insufficient data to draw clear conclusions about potentially important subgroup differences. Only one study (Coppen 2000) has examined male/female differences in the response to folate augmentation. This trial carried out a secondary analysis which found a clear benefit of folate augmentation in female patients but not in male patients. There was statistically significant heterogeneity between the subgroups. Effects of augmentation of similar magnitude were seen both for folate deficient subjects and those with normal blood results, although of note the treatment of the folate deficient population was over a longer time period - six months rather than twelve weeks.

Reviewers’ conclusions

Implications for practice
The currently available evidence suggests that folate supplementation may be effective when used in addition to conventional antidepressant medication. The evidence does not support the use of folate as a replacement for antidepressant medication in the treatment of depression. There is no evidence that supplementation is only effective in those with low folate results. There is as yet not enough evidence of a qualitative difference in response by sex to make clear cut conclusions about the absence of an effect of folate supplementation in male patients.

Implications for research
The available evidence raises the possibility that folate may have therapeutic potential as an augmentation strategy in the treatment of depressive disorder. Further randomised trials are required to establish the exact magnitude of the main effect and these will need to be adequately powered to investigate the possibility of subgroup effects, such as differences by gender, or by the presence or absence of folate deficiency. The benefits of addition of folate in cases of non-response to conventional antidepressants have yet to be investigated.

References

References to studies included in this review
Coppen 2000 {published data only}
Goffrey 1990 {published data only}
Passeri 1991 {published data only}

References to studies excluded from this review
Bell 1992
Carney 1970
Carney MW, Sheffield BF. Associations of subnormal serum folate and vitamin B12 values and effects of replacement therapy. Journal of Nervous & Mental Disease 1970;150:404-12.
Coppen 1986
Guaraldi 1993
Procter 1991

Additional references
Agnoli 1976

Ongoing studies
Reynolds
unknown .-.

AHCPR 1999

Berlin 1979

Botz 1979

Botz 1982

Bottiglieri 1984

Carney 1967

Carney 1990

Caruso 1984

Clayton 1986

CNCG 1992

Coppen 1989

Czeizel 1992

Fava 1997

Geddes 2001

HLTC 1998

Hyland 1988

Jenkins 1997

Kaufman 1981

Kaufman 1991

Lee 1998

MRC VSRG 1991

Murray 1997a

Murray 1997b

Regier 1988

Reynolds 1970

Regier 1971

Reynolds 1976

Sackett 1997

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Passeri 1991 {published data only}


* indicates the major publication for the study

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Clayton 1986

CNCG 1992

Coppen 1989

Czeizel 1992

Fava 1997

Geddes 2001

HLTC 1998

Hyland 1988

Jenkins 1997

Kaufman 1981

Kaufman 1991
Kaufman S. Some metabolic relationships between bipterin and folate: Implications for the "methyl trap hypothesis". Neurochemical
Lee 1992

Lee 1998

MRC VSRG 1991

Murray 1997a

Murray 1997b

Regier 1988

Reynolds 1970

Reynolds 1971

Reynolds 1976

Sackett 1997