Folate Augmentation of Treatment – Evaluation for Depression (FolATED): randomised trial and economic evaluation

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Declared competing interests of authors: Andrew McCaddon is a scientific advisor and shareholder of COBALZ Ltd – a private limited company developing novel B vitamin and antioxidant supplements.

Published July 2014
DOI: 10.3310/hta18480

Scientific summary

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Health Technology Assessment 2014; Vol. 18: No. 48
DOI: 10.3310/hta18480

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Introduction

Depression is a prevalent and debilitating mental disorder. It often persists or recurs throughout life. Guidelines recommend antidepressants for moderate to severe depression, but only half of sufferers respond to initial treatment. Research is necessary to investigate ways of augmenting antidepressants to improve this.

Folic acid may enhance antidepressant treatment for three reasons:

1. Patients with depression often have folate deficiency.
2. Folate deficits correlate with severity of depression and poor response to treatment.
3. Folate is needed to synthesise neurotransmitters linked to depression.

Aim and objectives

The relevant Cochrane review recommended large randomised trials to investigate the therapeutic potential of folate augmentation of antidepressants. The National Institute of Health Research (NIHR) programme commissioned FolATED (Folate Augmentation of Treatment – Evaluation for Depression) to address this gap in knowledge. Our main objectives were to assess the clinical effectiveness and cost-effectiveness of adding folic acid to antidepressant treatment of moderate to severe depression. Our secondary objectives were to investigate whether baseline folate and homocysteine predict response to treatment, and whether response to treatment depends on genetic polymorphisms related to folate metabolism.

Design

FolATED was a double-blind, placebo-controlled, yet pragmatic, randomised trial. To yield 80% power at 5% significance level of detecting a 'small' effect size of 0.3 – equivalent to a difference between groups of three points on the Beck Depression Inventory version 2 (BDI-II) – we sought to analyse 358 participants. To allow for losses across three assessments, we aimed to randomise 453. We exceeded both targets. We undertook cost–utility analysis from the perspective of the health and personal social services. We also extracted genomic DNA from blood provided by each participant to test whether polymorphisms change the effectiveness of folic acid combined with antidepressants.

Settings

Clinical Three centres in Wales: North East Wales, North West Wales and Swansea, Swansea, UK.

Trial management, including telephone randomisation The Registered Clinical Trials Unit in Bangor University, Bangor, UK.

Biochemical analysis University Hospital of Wales, Cardiff, UK.

Genetic analysis University of Liverpool, Liverpool, UK.

Participants

Patients over 18 years old presenting to primary or secondary care with confirmed moderate to severe depression for which they were taking or about to start antidepressant medication (ADM), and able to consent and complete assessments, but not:

a. folate deficient, vitamin B_{12} deficient, or taking folic acid or anticonvulsants
b. misusing drugs or alcohol; or suffering from psychosis, bipolar disorder, malignancy or other unstable or terminal illness; or
c. pregnant or planning to become pregnant.

Interventions

All participants followed pragmatic management plans initiated by a trial psychiatrist and maintained by their general practitioners. Once a day for 12 weeks participants in the experimental group added 5 mg of folic acid to their antidepressants, and those in the control group added an indistinguishable placebo; neither group knew whether their adjunct was folate or placebo.

Main outcome measures

Assessed at baseline ('week 0'), and 4, 12 and 25 weeks thereafter:

Mental health BDI-II (primary), Clinical Global Impression (CGI), Montgomery–Åsberg Depression Rating Scale (MADRS), UKU side effects scale, and Mini International Neuropsychiatric Interview (MINI) suicidality subscale.

General health UK 12-item Short Form Health Survey (SF-12; both mental and physical components), European Quality of life scale – 5 Dimensions (EQ-5D).

Haematology Serum folate, B_{12}, homocysteine.

Compliance Morisky Questionnaire.

Resource use Client Service Receipt Inventory.

Results

We recruited participants in three centres – North East Wales, North West Wales and Swansea – between July 2007 and November 2010, and completed follow-up in May 2011. The trial received 1488 referrals; screened 863, of whom 635 consented to take part; and randomised 479, of whom 475 were valid. Of 156 consenters not later randomised, 68 dropped out between screening and randomisation, and 36 reported better BDI-II scores at randomisation interview. Of 237 randomised to folic acid, eight withdrew within 4 weeks and six never attended appointments; of 238 randomised to placebo, 10 withdrew and 11 never attended. We analysed the remaining 440 (93% of the 475 valid randomisations), if necessary by statistically imputing missing data.

Clinical effectiveness

The main analysis focused on the 'area under the curve' (AUC) of each of the 13 main outcomes – BDI-II (primary), MADRS, CGI (three scales), EQ-5D (two scores), SF-12 (two scales) and UKU (four scales) – adjusted for stratification variables and the baseline score of that variable. The only significant result favoured the

placebo in the SF-12 Mental Component Score (MCS). Five of the non-significant differences favoured placebo and seven favoured folate.

The 33 adverse events (AEs) reported in the folic acid arm did not differ significantly from the 45 reported in the placebo arm. We adjudged six of those in the folic acid arm to be serious, compared with 14 in the placebo arm – another difference not statistically significant. We classified four of the AEs reported in the intervention arm as adverse reactions because folic acid (if prescribed) was a possible cause, in comparison with three in the control arm – also not statistically significant. Fortunately none of these reactions was serious or unexpected.

We assessed adherence to trial medication at 12 weeks in four ways: we found no significant differences in scores on the Morisky Questionnaire or in the number of returned pills; we found that 83% of those taking folic acid achieved adherence defined as a serum folate greater than 15 mg/ml, and 60% achieved adherence defined as reduction of at least 15% in serum homocysteine between baseline and 12 weeks.

To test the sensitivity of our main analyses to the assumption that AUC is a valid summary of the various outcome measures over 6 months, we repeated them in the form of repeated measures analyses of variance. We also applied this technique to serum folate, red cell folate, homocysteine and serum B_{12}. These last four analyses summarise a wide range of biochemical predictors of folate metabolism. By analysing and reporting interactions between 'treatment allocated' and 'time', they show that added folic acid has statistically very significant effects on serum folate and homocysteine; a marginal but not significant effect on red cell folate; but no independent effect on B_{12}.

Cost-effectiveness

There were no differences in resource use or resulting costs between treatment groups. The largest component was for psychiatric services (£797 in the folic acid group and £886 in the placebo group). Costs differed more in the 3 months before baseline: £514 in the folic acid group compared with £746 in the placebo group. As this difference may reflect an imbalance in patient or disease characteristics, our primary cost analysis used regression to adjust for these baseline differences.

In responding to the EQ-5D at baseline, most patients described themselves as having difficulty with anxiety or depression (97% in both groups), pain or discomfort (about 60% in both), and usual activities (about 78%). Between baseline and 6 months those reporting anxiety or depression fell to 75% in both groups, and difficulty with usual activities to about 58%. The resulting utilities rose from 0.482 at baseline to 0.605 at 6 months in the folate group, and 0.514 to 0.607 in the placebo. After adjusting for differences at baseline, we found no significant differences between treatment groups in quality-adjusted life-years (QALYs) gained – as estimated by EQ-5D (primary analysis), EQ-VAS or SF-12 via Short Form Health Survey – 6 Dimensions (SF-6D); or in outcomes for the cost-effectiveness analyses – notably area under the BDI-II curve. Thus folic acid seems no more effective, but no more expensive, than placebo.

Biochemistry

Despite the lack of clinical response to folic acid, it was effective in increasing participants' folate and in reducing homocysteine. Nevertheless the few patients who had very low baseline red cell folate yielded weak but consistent evidence across multiple instruments that augmenting antidepressants with folic acid improved clinical outcome. However biochemical variables predicted only one of the eight clinical outcomes – the CGI improvement scale.

Genetics

We analysed associations between 104 relevant single nucleotide polymorphisms (SNPs) and each of seven outcome measures – BDI-II, MADRS, CGI severity, EQ-5D, EQ-VAS, SF-12 mental and SF-12 physical. We found two statistically significant main effects. The rs11627525 SNP in the methylenetetrahydrofolate dehydrogenase 1 (*MTHFD1*) gene was associated with MADRS scores [false discovery rate (FDR) = 4.67%; significance level $p = 0.04$] but none of the other six outcome measures analysed. The rs588458 SNP in the

folate hydrolase 1 (*FOLH1*) gene was associated with EQ-5D utilities (FDR = 3.37%; $p = 0.03$) but none of the other measures. We also found one statistically significant SNP-treatment interaction – that between the rs17102596 SNP in the methionine adenosyltransferase 1 alpha (*MAT1A*) gene and folic acid influenced SF-12 mental status (FDR = 2.55%; $p = 0.02$).

Discussion

Summary

Clinical effectiveness

FoLATED shows that routinely adding 5 mg of folic acid to ADM has no clinical benefit. This finding is very consistent across outcome measures and time points. The one exception is the MCS of the SF-12, which shows a statistically significant difference favouring placebo, especially at 12 weeks. However there were no significant differences in reported side effects or (serious) AEs between groups.

Cost-effectiveness

No economic criterion was significant: folic acid saved only £48 per patient; folic acid gained only three EQ-5D-adjusted days per patient, while EQ-VAS showed a very small loss. We conclude that folic acid is not cost-effective.

Biochemistry

Folic acid was effective in increasing participants' folate. However biochemical variables predicted only one of the eight chosen clinical outcomes.

Genetics

FolATED identified only two polymorphisms within genes of the one-carbon folate pathway associated with clinical outcome regardless of treatment, and one such polymorphism associated with the outcome of folic acid. However these polymorphisms could not replicate these associations with any other outcome measure, including the primary outcome. Furthermore one polymorphism associated with depression in previous studies did not modify the effect of either antidepressant therapy or folic acid supplementation. We judge this consistent with the trial finding that folic acid does not influence the treatment of depression. In future a whole-genome approach to the FolATED data could identify markers of efficacy beyond those already analysed.

Strengths and limitations of FolATED

FolATED is by far the largest trial to evaluate folic acid in augmenting ADM. We powered it to detect a clinically small difference between treatment groups, and followed rigorous procedures for randomisation and blinding. We recruited a wide range of patients treated for moderate or severe depression in primary or secondary care. There were few exclusion criteria, and our sample included comorbidities like substance misuse, often excluded from less pragmatic trials.

Of our sample 36% achieved 'response to treatment', namely 50% reduction in BDI-II baseline score; 27% achieved 'remission' at 6 months, namely BDI-II score less than 13; and ADM reduced depressive symptoms markedly over the first few weeks, then more slowly until 6 months. All these findings were expected from a study mixing new and continuing treatment episodes. Hence the lack of any effect of folic acid is not attributable to unusual treatment resistance to antidepressants in our sample. In short FolATED was both robust and representative.

Interpretation

Clinical effectiveness

Our negative outcomes contrast with positive findings in smaller trials. For example Coppen and Bailey reported a significantly greater reduction in Hamilton Depression Rating Scale (HDRS) scores with fluoxetine and 400 mg of folic acid than with fluoxetine and placebo, but only in females (Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: randomised, placebo controlled trial. *J Affect Disord* 2000;**60**:121–30.). However their sample was much less representative than that recruited by FolATED. Furthermore, while FolATED took care at all stages to avoid unblinding researchers, Coppen and Bailey seemed less rigorous, especially in handling blood results.

Biochemical interpretation

Folate is a naturally occurring B vitamin, needed in the brain to synthesise serotonin, noradrenaline and dopamine. In humans the biologically active form is methylfolate – derived from ingested folates, taken up by cells and transported to the cerebrospinal fluid (CSF) via folate receptors. Folic acid is an inactive form of folate not naturally found in the human body, which needs transformation to methylfolate. There is evidence that commercial preparations of folic acid can compete with methylfolate for folate receptors, thus exacerbating folate deficiency in the central nervous system (CNS). Hence our finding that folic acid had a statistically significant negative effect on the widely used SF-12 MCS may reflect folate deficiency rather than type 1 error.

Thus better understanding of the one-carbon folate pathway has raised questions about the most appropriate formulation of folate to use for folate deficiency. Stahl argues that methylfolate is therapeutically better than folic acid as it does not need transformation, which may be difficult for some patients (Stahl SM. Novel therapeutics for depression: L-methylfolate as a trimonamine modulator and antidepressant-augmenting agent. *CNS Spectr* 2007;**12**:739–44). Furthermore high doses of inactive folic acid may compete with methylfolate for transport across the blood–brain barrier.

Against this biomedical background our rigorous and powerful trial has established that folic acid has no general role as adjunct in antidepressant therapy. However studies in patients with cardiovascular disease have shown that higher doses of folic acid produce greater concentrations of methylfolate in plasma. Moreover the reductions in homocysteine in participants on folic acid relative to those on placebo suggests that they were successfully metabolising folic acid to methylfolate. Nevertheless we suspect that the beneficial increase in methylfolate was masked by excess folic acid that competed for the folate receptors and led to negative results. Before we dismiss all folates, however, we recommend an updated systematic review and meta-analysis, ideally at patient level, of the many trials of folate augmentation.

At the time of our initial proposal little information was available on the use of methylfolate in patients with depression. Now there is evidence that methylfolate given as adjunct or monotherapy reduces depressive symptoms in patients with low folate levels or alcoholism, and improves cognitive function and depressive symptoms in elderly patients with dementia and folate deficiency. Furthermore there are long-standing concerns that folate may increase cancer risk, mask B_{12} deficiency and exacerbate depressive symptoms. As methylfolate may reduce some of these risks, it may now be a candidate for a large multi-centre trial. In that context we offer the design of FolATED as a proven model. In hindsight, however, we judge that a trial recruiting for 1 year in 10 centres would yield better value for money than one recruiting for 3 years in three centres.

Conclusions

This rigorous and powerful trial has established that folic acid is not an effective adjunct to antidepressant therapy.

The NIHR commissioned FolATED at a time when there was considerable scientific interest in the role of folate in causing and treating depression. Since then this interest has grown, with increasing international pressure to use folate as an adjunct to antidepressants and in algorithms for treating depression. The unequivocally negative findings of FolATED demand reappraisal of this consensus and associated treatment guidelines.

There is a strong case for appraising whether future trials of methylfolate would yield value for money.

Trial registration

This trial is registered as ISRCTN37558856.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 5.116

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index and is assessed for inclusion in the Database of Abstracts of Reviews of Effects.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 04/35/08. The contractual start date was in October 2006. The draft report began editorial review in May 2012 and was accepted for publication in August 2013. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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