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Brief report

Folic acid supplementation for prevention of mood disorders in young people at familial risk: A randomised, double blind, placebo controlled trial

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ABSTRACT

Background: Clinical mood disorders often become clinically manifest in the later teenage years and early twenties and can be associated with a poor long-term prognosis. The primary prevention of these disorders would therefore have great public health value. Nutritional supplements are a feasible intervention for primary prevention and several epidemiological studies have indicated links between low folate status and depressive symptomatology in the general population.
Method: A randomised, double blind, parallel group, placebo-controlled trial in which participants, aged 14–24 years, at increased familial risk of mood disorder, were randomised to folic acid (2.5 mg daily) or identical placebo liquid for a maximum of 36 months. Primary outcome data (the onset of a DSM-IV mood disorder) were collected from 112 participants; 56 per group.
Results: The incidence of mood disorder in the folic acid and placebo groups were 14.3% and 17.9% respectively, a non-significant difference. However, there was post-hoc evidence that folic acid delayed the time to onset of mood disorder in those participants who became unwell.
Limitations: Small sample size and rate of onset of mood disorders lower than expected.
Conclusions: Although long term folic acid supplementation was well tolerated, with high levels of adherence, there was no evidence that it reduced the incidence of mood disorder compared to those taking placebo.

1. Introduction

Recurrent major depression and bipolar disorder are life-long illnesses that often become clinically apparent in the late teenage years or early twenties (Angst, 2000). Treatment for depression and bipolar illness is usually initiated after the onset of a clinically significant mood disturbance, i.e. during an episode of major depression or hypomania. Strategies at this point include pharmacological and psychological treatment of the acute mood disturbance. Subsequently, various forms of medical treatment are often continued for substantial periods of time. despite this, the longer-term prognosis of mood disorder in teenagers and young people is poor (Angst, 2000), and there is particular concern about the safety of psychotropic medication in young people (Ramchandani, 2004; Morrison et al., 2012).

An important reason for this poor prognosis is that episodes of mood disturbance themselves appear to play a role in worsening outcome. For example, a number of physiological abnormalities associated with depression may persist after symptom resolution, suggesting that depression may cause a kind of biological "scarring" of the brain that can predispose to further episodes of illness (Bhagwagar and Cowen, 2008). Similarly, the psychosocial consequences of mood disorder in young people can be profound and include withdrawal from peer relationships, poor academic achievement and an increased liability to experience stressful adverse life events (Greden, 2001; Harrington and Dubicka, 2001).

These data suggest that there may be important benefits in identifying a relatively straightforward intervention, which could delay the onset or preferably prevent mood disturbances, during adolescence. Nutritional supplements are a feasible intervention for primary prevention because they are likely to be acceptable and intuitively would seem to have a greater chance of being effective at a preventative stage, rather than later when clinical mood disturbances have occurred. For example, folate supplements can prevent neural tube defects but are not a useful treatment for those who already possess the condition.

Folate is a general term for a group of water soluble B vitamins, also known as B9 and is found in leafy vegetables like spinach. Folic acid is the oxidised synthetic compound used in food

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fortification and dietary supplements. Although similar in structure, the body absorbs folic acid more easily than folate.

Relative folate deficiency is known to be associated with several neuropsychiatric disorders including mood disorder and there are a number of plausible mechanisms by which folate deficiency might produce neurobiological changes relevant to the development of mood disorder (Mattson and Shea, 2003). For example, folate is important in preventing the accumulation of homocysteine, which, in excess, can promote nerve cell death (Mattson and Shea, 2003).

Low plasma and red blood cell folate have long been associated with clinical depressive disorders. A meta-analysis showed a significant relationship between low folate status and risk of depression (Gilbody et al., 2007) and treatment with folic acid has been shown to improve the therapeutic effect of fluoxetine in depressed patients (Coppen and Bailey, 2000; Venkatasubramanian et al., 2013). Moreover, long-term treatment of post stroke survivors with folic acid, B6, and B12 was associated with a reduction in the hazard of major depression (Almeida et al., 2010).

The present study was designed to provide a preliminary test of the hypothesis that folic acid supplementation given to young people at increased familial risk of mood disorder may convey a neuroprotective effect, enabling vulnerable individuals to negotiate maturational and social stresses of young adulthood without the development of clinical mood disorders. Thus the primary objective of the study was to determine whether folic acid supplementation could prevent first episodes of clinical mood disorder in euthymic young people at increased risk of mood disorder by virtue of having a parent with either recurrent major depression or bipolar disorder. A secondary objective was to determine whether, in these young people, folic acid could improve depression scores on the Mood and Feeling Questionnaire (MFQ) (Wood et al., 1995).

2. Methods

2.1. Study design

The study, Prevention of Mood Disorders by Folic Acid Supplementation (PRE-EMPT), was a randomised, placebo-controlled, parallel group, double blind study. Participants initially entered a run-in phase during which they took folic acid oral solution in the form of "Lexpec" manufactured by Rosemont Pharmaceuticals (PL 00427/0034) (2.5 mg) daily for four weeks. The dose of folate required to produce a maximal lowering of plasma homocysteine is about 1.0 mg daily, but to prevent neural tube defect, particularly in those at risk, higher doses of up to 5 mg a day are more effective (Wald et al., 2001). This suggests that in certain circumstances doses of folate substantially above what would be regarded as the usual nutritional requirement (about 400 mg daily) can produce clinically crucial neuroprotective effects. In addition, the neuroprotective effect of folate is not likely to be attributable only to lowering of homocysteine. For this reason we decided in this study to employ a dose of folic acid of 2.5 mg daily. This dose is available in the form of syrup which is licensed in the UK for the treatment of folate deficiency conditions.

The purpose of the run-in was to check whether participants would be likely to both tolerate and maintain compliance with folic acid/placebo treatment during the longer-term study. If satisfactory compliance was maintained during the active run-in and participants declared that they were willing to continue with folic acid/placebo treatment, they were then randomised to one of two treatments in a parallel group design (a) folic acid as "Lexpec" (2.5 mg daily) or (b) identical placebo liquid. They were encouraged to take this at the same time each day, at a time most convenient for them e.g. first thing in the morning before cleaning teeth. If they forgot to take it they were instructed to report this as a "missing dose". A web-based algorithm was used which was accessed by researchers online; thus a randomisation number for each participant was generated, taking into account the minimisation requirements and the appropriate blinded medication was assigned. Access to the randomisation code was limited to the trial programmer; all other researchers remained blind throughout the trial and analysis. The treatment period was up to 36 months.

2.2. Participants

We aimed to recruit 200 participants to the run-in phase, with 120 participants entering the randomised phase. This number takes into account that active run-ins to exclude non-compliant individuals usually exclude up to 30% of those screened (Pablos-Mendez, 1998). Entry criteria stipulated that participants were male and female, 14–24 years of age, who had a biological parent with a life-time history of recurrent major depression, bipolar I or bipolar II disorders. Family history was assessed using the family history method (Andreasen et al., 1986). Parents, apart from participants under 16, were not contacted directly; however most participants informed their parents of their inclusion in the trial. Participants were identified using several approaches: offspring of known patients with depression and bipolar disorder; via a University student survey, advertising in the press, online and posters. This was a single centre trial based in Oxford, UK and the study was approved by the National Research Ethics Committee.

Participants were excluded if they had a current or past DSM-IV Axis I disorder. This was assessed using the Structured Clinical Interview for DSM-IV (SCID) (American Psychiatric Association, 2000). Current sub-syndromal mood disorder was not a reason for exclusion but was assessed and used in the minimisation process. Participants were excluded if they possessed a significant current medical condition, such as epilepsy, or if they were already using folate supplements and were unwilling to give them up for the duration of the study. All subjects gave informed written consent to the study and a parent or guardian also gave written consent where subjects were under 16 years of age. To ensure balance between the groups the trial was minimised for gender, age, sub-syndromal mood symptoms and parental diagnoses of depression or bipolar disorder.

2.3. Ratings and follow-up

On entry to the study, subjects completed the MFQ, a 32-item scale designed to detect and monitor depression in adolescents in the community (Wood et al., 1995). The MFQ was completed monthly while participants remained in the study. Each of the 32 items on the MFQ is scored on a 3-point scale, and the sum of all answered items gives the total MFQ score (range: 0–66). The higher the MFQ score, the higher the levels of depression symptoms. Other self-report questionnaires completed at screening included the Altman Self-Rating Mania Rating Scale (Altman et al., 1997), the Neurotic subscale of the Eysenck Personality Questionnaire (EPQ) (Eysenck and Eyesenck, 1975), the Responses Style Questionnaire (RSQ) (Nolen-Hoeksema, 1991) and the Children's Attributional Style Questionnaire-Revised (CASQ-R) (Thompson et al., 1998). The RSQ measures the tendency to ruminate, while the CASQ-R assesses the kinds of causal attributions children give to positive and negative life events. Both web-based assessments and paper forms were available, depending upon participant preference. If monthly returns aroused concerns the participant was contacted and interviewed. At six monthly intervals all participants were re-interviewed with the SCID. The primary endpoint was the occurrence of an episode of Axis 1 mood disorder on DSM-IV. Compliance was determined by bottle return, 6 monthly

interviews and monthly online recording by participant of number of missed doses.

2.4. Statistical analysis

Over three years the incidence of new cases of mood disorder in this high-risk group would be expected to be approximately 10% annually or about 30% overall (Beardslee et al., 1998; Delbello and Geller, 2001). If 60 participants per group were retained over the course of the trial, the study would have a power of 0.8 to detect a 20% reduction in the incidence of major clinical mood disorder. A similar power would detect a mean overall decrease of five points on the MFQ, representing a clinically meaningful reduction in depressive symptomatology.

Analysis was by intention to treat. Data for the primary outcome for participants who were lost to follow up (LTFU) were censored at time of their last visit. For other outcomes endpoint data, participants who were LTFU were imputed using Last Observation Carried Forward (LOCF). In order to analyse the primary objective a Kaplan–Meier survival plot was performed. This is an estimate of the survival function in a series of horizontal steps of declining magnitude which, when a large enough sample is taken, approaches the true survival function for that population. An advantage of the Kaplan–Meier curve is that the method can take into account some types of censored data, particularly right-censoring, which occurs if a patient withdraws from a study, i.e. is lost from the sample before the final outcome is observed. A repeated measures General Linear Model (GLM) was performed on 36 months of MFQ data using an intention to treat analysis.

3. Results

3.1. Participant disposition and demographics

The recruitment start date was 13.12.2005 and recruitment end date was 27.04.2010. Following pre-screening by email or phone, a total of 124 participants attended a screening interview, of which 121 were included in the run-in phase of the study (Fig. 1). Following randomisation, no participant withdrew due to side effects. Monthly reporting of illnesses, medications and potential side effects elicited no adverse effect of the folic acid/placebo syrup apart from an aversion by some participants to the artificial strawberry taste.

Randomisation and primary outcome data were collected from 112 participants; active, $n=56$ (39 females, mean length of time in study 23.2 ± 10.0 months, range 4–36 months); placebo, $n=56$ (39 females, mean length of time in study 20.0 ± 12.9 months, range 1–36 months). The groups were well matched for demographic psychosocial data and compliance (Table 1). Twelve participants in each group had a parent with bipolar disorder; the remaining affected parents had recurrent major depression.

3.2. Primary end point

Eighteen participants (16%) reached the primary endpoint of the trial i.e. the occurrence of an episode of DSM-IV Axis 1 mood disorder as determined by the SCID. The incidence of mood disorder in the folic acid and placebo groups were 14.3% and 17.9% respectively. Our data showed that there was no significant

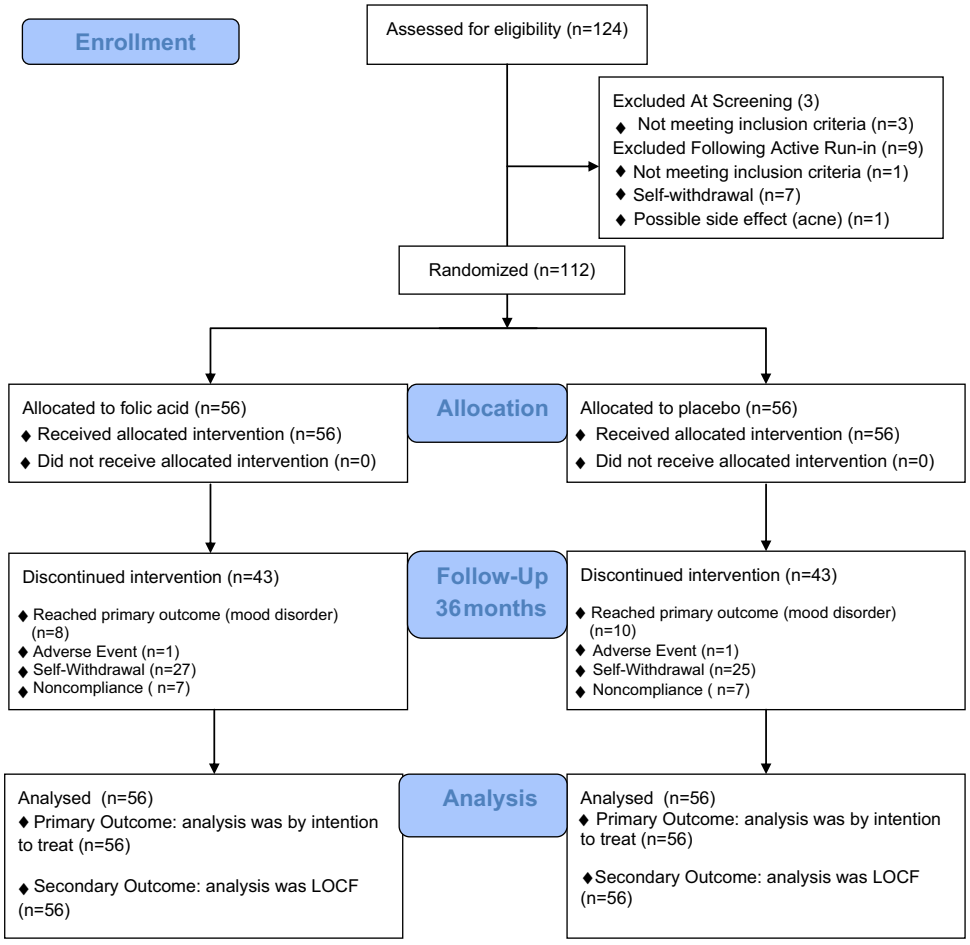

Fig. 1. CONSORT flow diagram.

Table 1
Baseline demographic and psychosocial questionnaires plus compliance between folic acid and placebo groups.

	Folic acid	**Placebo**	Difference of means (SEM)	95% CI	*p* Value (unpaired *t*-test)
	Group mean ± SD	Group mean ± SD			
Sub-syndromal symptoms	25 (44.6%)	23 (41.1%)	–	–	0.70[a]
Age	18.9 ± 2.3	18.6 ± 1.7	0.3 (0.4)	−0.5 to 1.0	0.54
Alcohol (units/week)	5.7 ± 6.6	6.5 ± 5.8	−0.7 (1.2)	−0.3 to 1.6	0.51
Cigarettes/day	0.46 ± 1.5	0.18 ± 0.9	0.3 (0.2)	−0.2 to 0.8	0.23
No bottles issued	26.9 ± 10.5	23.3 ± 13.1	3.6 (2.2)	−0.8 to 8.1	0.11
Maximum bottles used	25.0 ± 10.6	20.7 ± 13.1	4.3 (2.2)	−0.2 to 8.7	0.06
Missed doses (%)	8.8 ± 6.6	10.7 ± 8.0	−1.9 (1.4)	−4.8 to 8.7	0.17
MFQ	10.9 ± 7.9	11.9 ± 9.5	−1.0 (1.6)	−4.3 to 2.3	0.55
Altman	3.9 ± 3.0	4.9 ± 3.9	−1.0 (0.7)	−2.3 to 0.3	0.13
EPQ-N	11.9 ± 4.7	12.6 ± 5.7	−0.6 (1.0)	−2.6 to 1.3	0.50
CASQ-R	3.7 ± 3.7	3.6 ± 3.5	0.1 (0.7)	−1.3 to 1.4	0.92
RSQ	24.0 ± 10.7	25.1 ± 12.3	−1.1(2.2)	−5.4 to 3.3	0.63

MFQ=Mood and Feeling Questionnaire; Altman=Altman Self-Rating Mania Scale; EPQ-N=Eysenck Personality Questionnaire-Neurotic subscale; CASQ-R=Children's Attributional Style Questionnaire-Revised; RSQ=Responses Style Questionnaire.

[a] Chi square test.

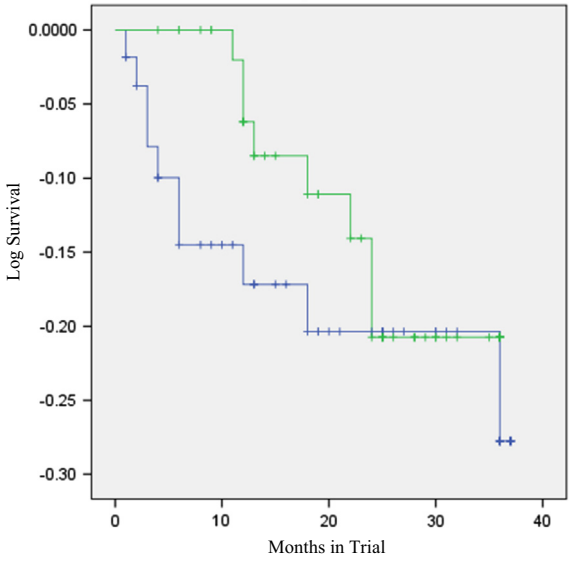

Fig. 2. Kaplan–Meier survival plot for placebo-treated (blue) and folic acid treated (green) participants (n=56 per group) No significant difference in survival time between the folic acid and placebo groups (Log Rank (Mantel–Cox) Chi-square: 0.676; df: 1, p=0.41).

difference in survival time between the folic acid and placebo groups (Log Rank (Mantel–Cox) Chi-Square: 0.676; df: 1, p=0.41) (Fig. 2). However, in a post-hoc analysis only examining the 18 participants who reached the primary endpoint, the median time to the onset of the mood disorder was 5 months in the placebo group and 15.5 months in the folate group (p=0.023, Mann–Whitney U test). In the folic acid group two participants met criteria for major depressive episode while six were diagnosed as depressive disorder not otherwise specified. In the placebo group four participants were diagnosed with major depressive episode while one had bipolar 1 disorder. One had major depression with psychotic disorder not otherwise specified. The remaining four subjects were diagnosed as depressive disorder not otherwise specified.

3.3. Secondary end point

There was no main effect of folic acid treatment on MFQ scores (F=0.76; p=0.39) or time (F=1.55; p=0.1) and no treatment by time interaction (F=0.19; p=0.46). Analysing MFQ data for the first 12 months similarly showed no effect of treatment, time or treatment by time interaction (all p values > 0.1).

3.4. Predictors of depression

In keeping with previous studies (Roberts and Kendler, 1999; Hettema et al., 2006; Kuehner and Weber, 1999; Broderick and Korteland, 2004; Nolen-Hoeksema et al., 1986), the participants who became depressed were found at baseline to have higher scores on the EPQ-N and RSQ and lower scores on the CASQ-R (Table 2).

4. Discussion

The principal finding of our study is that folic acid treatment did not reduce the incidence of mood disorder in a group of participants at increased familial risk of depression and bipolar illness. There was, however, a hint from a post-hoc analysis that folate may have delayed the onset of an episode of mood disorder in those people in whom it occurred. In addition, the mood disorders in the folate treated participants, when they occurred, tended to be clinically milder. Thus we cannot exclude that a larger participant sample or different experimental design would have shown a significant beneficial effect of folate prophylaxis.

The incidence of mood disorders in the folic acid and placebo groups were 14.3% and 17.9% respectively, approximately half the predicted rate. It could be that our group of mainly high achieving university students were not as susceptible as other high risk young people to developing a mood disorder. Moreover, the group was a self-selecting group and it is possible that those that consented to take part were more able to cope with life than those who declined. In addition, our participants were generally 18 years or over, and may have passed the most vulnerable teenage years. Finally, the mean length of time of participants in the study was a little under 2 years; therefore with a 10% annual risk of depression our observed incidence rates are, in fact, reasonably compatible with the expected percentage.

It was noteworthy that a number of psychosocial risk factors, previously reported to be associated with the development of depression, were more frequent in the subgroup of participants who did go on to experience clinical mood disturbance subsequently. For example high neuroticism is widely regarded as a risk factor for depression (Roberts and Kendler, 1999; Hettema et al., 2006), and ruminative thinking style as measured by the RSQ

Table 2
Baseline demographic and psychosocial questionnaires between participants reaching a DSM-IV diagnosis during the trial compared to participants that did not meet criteria.

	DSM-IV diagnosis ($n=18$)	**No DSM-IV diagnosis ($n=94$)**	Difference of means (SEM)	95% CI	p Value (unpaired t-test)
	Group mean ± SD	Group mean ± SD			
Subsyndromal symptoms	10 (55.6%)	38 (40.4%)	–	–	0.23[a]
Age	18.5 ± 1.7	18.8 ± 2.0	−0.3 (0.5)	−0.7 to 1.3	0.52
MFQ	15.0 ± 12.5	10.7 ± 7.6	4.3 (3.1)	−10.6 to 2.1	0.17
Altman	4.8 ± 4.1	4.4 ± 4.4	0.4 (0.9)	−2.3 to 1.3	0.59
EPQ-N	15.2 ± 5.1	11.6 ± 5.0	−3.6 (1.3)	−6.1 to −0.9	0.008
CASQ-R	1.9 ± 3.8	4.0 ± 3.4	−2.1 (0.9)	0.3 to 3.9	0.038
RSQ	29.5 ± 8.2	23.6 ± 11.8	−5.9 (2.3)	−10.6 to −1.2	0.015

For abbreviations see Table 1.

[a] Chi square test.

predicts a poorer outcome and higher risk of recurrence in patients with depression (Kuehner and Weber, 1999). Also, in adolescents, ruminative thinking on the RSQ predicted levels of depression at follow-up (Broderick and Korteland, 2004). Similarly on the CASQ-R, attribution of negative life events to fixed "internal" factors related to the self has been reported to be linked with the development of depression (Nolen-Hoeksema et al., 1986). Interestingly, at the onset of the study the two treatment groups did not differ significantly in terms of scores of neuroticism, ruminative thinking and attribution on the CASQ-R, which shows the utility of these psychosocial measures in prediction of vulnerability to the onset of mood disorder.

It might be asked whether folic acid treatment could produce greater prophylactic effects in subgroups of participants, perhaps those with low serum folate levels prior to treatment or certain polymorphisms of the enzymes involved in folate metabolism (Bjelland et al., 2003; Lewis et al., 2006). This was designed to be a pragmatic study so we did not stratify people for such variables but they would be worth considering in future investigations of the utility of folic acid in the acute treatment and prevention of depression. Other explanations for the lack of response are also possible. For example, Hoffman (2011) discusses whether homocysteine plays a causal role in many pathologies with which it is associated, or alternatively, it is instead a marker for oxidative stress which may be the key mediator for many disorders. If the UK does fortify bread with folic acid it will be of great interest to see if this leads to a reduction in secular rates of depression.

5. Limitations

We recruited significantly fewer participants than we had planned (124 versus 200). This was mitigated to some extent by the fact that relatively few participants were excluded after the treatment run-in, either through poor compliance or personal choice. Therefore we were able to randomise a similar number of participants to that which we had intended. A second difficulty was that the rate of onset of episodes of mood disorder was less than we had anticipated (about 16% versus 30%) though as noted above this may be due in part to the reduced follow up time for most of the participants. This fact also resulted in the necessity to use LOCF and may have resulted in biases due to the missing data. Despite this, we were able to show that in patients who became ill that the time to presentation was apparently significantly lengthened by folic acid treatment. However this is a post-hoc finding and must be treated with caution.

Finally as noted above, we did not have pre-treatment measures of folate status in our participants or assessments of dietary folate intake. Clearly it is possible that folate supplementation might be effective in preventing depression only in those with relative folate deficiency and the design of our study would not have allowed such an effect to be demonstrated.

Conflict of interest

JRG has been an expert witness for Dr. Reddy's Laboratories and is Chief Investigator on the CEQUEL trial to which GlaxoSmithKline have contributed and supplied investigational drugs. PJC is a paid member of an advisory board for Lundbeck.

All other authors declare that they have no conflicts of interest.

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