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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