B vitamins to enhance treatment response to antidepressants in middle-aged and older adults: results from the B-VITAGE randomised, double-blind, placebo-controlled trial

Osvaldo P. Almeida, Andrew H. Ford, Varsha Hirani, Vash Singh, Frank M. vanBockxmeer, Kieran McCaul and Leon Flicker

Background
Depression is common and the efficacy of antidepressants is suboptimal. High plasma homocysteine has been consistently associated with depression, and treatment with certain B vitamins demonstrably reduces its concentration.

Aims
To determine whether vitamins B_{6, 12} and folic acid enhance response to antidepressant treatment over 52 weeks.

Method
Randomised, double-blind, placebo-controlled trial of citalopram (20-40 mg) together with 0.5 mg of vitamin B_{12}, 2 mg of folic acid and 25 mg of vitamin B_{6} for 52 weeks (Australian and New Zealand Clinical Trials Registry: 12609000256279). Participants were community-dwelling adults aged 50 years or over with DSM-IV-TR major depression. We measured severity of symptoms with the Montgomery–Asberg Depression Rating Scale (MADRS). The primary outcome was remission of the depressive episode after 12, 26 and 52 weeks. Secondary outcomes included reduction of MADRS scores over time and relapse of major depression after recovery by week 12.

Results
In total, 153 people were randomised (76 placebo, 77 vitamins). Remission of symptoms was achieved by 78.1 and 79.4% of participants treated with placebo and vitamins by week 12 (P = 0.840), by 76.5 and 85.3% at week 26 and 75.8 and 85.5% at week 52 (effect of intervention over 52 weeks; odds ratio (OR) = 2.49, 95% CI 1.12–5.51). Group differences in MADRS scores over time were not significant (P = 0.739). The risk of subsequent relapse among those who had achieved remission of symptoms at week 12 was lower in the vitamins than placebo group (OR = 0.33, 95% CI 0.12–0.94).

Conclusions
B vitamins did not increase the 12-week efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over 1 year. Replication of these findings would mandate that treatment guidelines adopt the adjunctive use of B vitamins as a safe and inexpensive strategy to manage major depression in middle-aged and older adults.

Declaration of interest
None.

Antidepressant medications are at the forefront of the management of depressive disorders in adults. Their use reduces the severity of symptoms and promotes the remission of depressive episodes, but as many as 50% of patients fail to respond satisfactorily to first-line antidepressant treatment. Attempts to augment response to antidepressants with other agents have produced inconsistent results, and findings have been difficult to generalise because of the characteristics of study samples (predominantly participants with treatment-resistant illness) and diversity of the approaches tested. This lack of success in enhancing the efficacy of antidepressant treatment is, in part, because of our fragmented understanding of the physiological pathways that lead to the development and maintenance of depressive symptoms. Nonetheless, advances have been made. A handful of clinical investigations in the 1960s reported that mental disorders, including depression, were associated with folate deficiency, a finding that was later confirmed by Reynolds and colleagues in a convenience sample of 101 British adults with depression. Subsequently, it became apparent that a large proportion of people with megaloblastic anaemia showed evidence of clinically significant depressive symptoms, either in association with deficiency of folate (vitamin B_{9}) or vitamin B_{12}, leading to suggestions that these B vitamins could potentially lie on the causal pathway that leads to depression. Folate is a co-substrate of various cell reactions involved in methylation and synthesis of nucleic acid and neurotransmitters, such as serotonin, dopamine and noradrenaline. The intracellular concentrations of folate and vitamin B_{12} can be inferred, indirectly, through the total plasma concentration of homocysteine (tHcy), which can be converted to methionine through an enzymatic reaction that uses 5-methyletetrahydrofolate as the methyl donor group. Consequently, the plasma concentration of homocysteine falls as the intracellular concentration of various folates and vitamin B_{12} rises. Numerous observational studies have since confirmed that depression, particularly in later life, is associated with relatively low concentrations of folate and vitamin B_{12}, as well as with high tHcy, although vitamin supplementation has negligible effects on the mood of adults and older adults free of clinically significant depressive symptoms.

A meta-analysis of genetic association studies showed that a common polymorphism of the methylenetetrahydrofolate reductase (MTHFR) enzyme that increases the basal concentration of tHcy also increases the risk of depression, suggesting that high tHcy lies on the causal pathway that leads to depression in later life. The findings of four small double-blind clinical trials published in the mid 1980s and 1990s were generally consistent with a causal relationship between high tHcy and depression: they reported that folate supplementation improves response to antidepressant treatment, albeit inconsistently. More recently, a secondary analysis of a randomised, placebo-controlled, double-blind trial of folate, vitamin B_{12}, and vitamin B_{9} to prevent cardiovascular events among stroke survivors showed that participants assigned
Method

Trial design

B-VITAGE was a 1-year parallel, randomised, double-blind, controlled trial of citalopram and adjunctive treatment with vitamins B<sub>6</sub>, B<sub>12</sub> and folate or placebo. The allocation ratio was 1:1. Three weeks after the trial commenced, the lower age limit of participants was decreased from 60 to 50 years to facilitate recruitment and increase the generalisability of findings. The Human Ethics Committee of the Royal Perth Hospital approved the study protocol and all participants provided written informed consent.

Participants

Eligibility criteria included: (a) age 50 years or over, (b) major depressive episode in the context of a major depressive disorder (single episode or recurrent) according to DSM-IV-TR criteria; (c) a Montgomery–Åsberg Depression Rating Scale (MADRS) score ≥20; (d) fluency in written and spoken English; (e) Alcohol Use Disorders Identification Test (AUDIT) ≤15; (f) Mini-Mental State Examination (MMSE) score ≥24; (g) negative clinical history for stroke or neurodegenerative diseases (such as Parkinson’s disease); (h) negative clinical history of allergic reactions to citalopram or escitalopram; (i) negative clinical history of life-threatening illness likely to compromise 1-year survival (such as metastatic cancer); (j) no evidence of prominent psychotic symptoms or suicidal intent; (k) negative clinical history for stroke or neurodegenerative diseases (such as coronary heart disease), chronic respiratory diseases (such as asthma or emphysema), diabetes, hearing impairment and history of past depression. More specifically, we asked: ‘Have you ever been told by a doctor that you had depression?’ Possible answers to this question were ‘yes’ or ‘no’. Participants maintained a medication diary for the duration of the study, where they recorded all medications consumed each day of the year (including changes of antidepressants). In addition, bottles containing the study tablets (citalopram for 12 weeks and vitamins/placebo for 52 weeks) were returned to the pharmacy at each assessment (4, 8, 12, 26 and 52 weeks) and the number of pills dispensed, consumed and returned were recorded. Individuals who had consumed at least 75% of the study tablets prescribed were considered to have adhered to treatment.

Outcomes

The primary outcome of interest of this study was remission of DSM-IV-TR major depressive episode after 12, 26 and 52 weeks of treatment, as assessed by the MINI. A reduction of 50% or more in the MADRS scores over the same period was another outcome of interest. Secondary outcomes included reduction of MADRS scores over time (4, 8, 12, 26 and 52 weeks), relapse of major depressive symptoms following remission by 12 weeks (26 and 52 weeks) and change from citalopram to another antidepressant.

We collected data on age (in years), gender, place of birth, marital status, past self-reported clinical history of cardiovascular diseases (such as coronary heart disease), chronic respiratory diseases (such as asthma or emphysema), diabetes, hearing impairment and history of past depression. More specifically, we asked: ‘Have you ever been told by a doctor that you had depression?’ Possible answers to this question were ‘yes’ or ‘no’. Participants maintained a medication diary for the duration of the study, where they recorded all medications consumed each day of the year (including changes of antidepressants). In addition, bottles containing the study tablets (citalopram for 12 weeks and vitamins/placebo for 52 weeks) were returned to the pharmacy at each assessment (4, 8, 12, 26 and 52 weeks) and the number of pills dispensed, consumed and returned were recorded. Individuals who had consumed at least 75% of the study tablets prescribed were considered to have adhered to treatment.

During the face-to-face assessments (weeks 4, 8, 12, 26 and 52) participants were asked about adverse effects experienced since their last visit, and rated their presence as ‘not at all or a little’ or ‘quite a bit or a lot’ for: tremor of the hands, muscle stiffness, involuntary muscle contractions, muscle cramps, pins and needles in the body, difficulty concentrating, agitation or restlessness, irritability, dizziness, fainting, headache, other pain, arthritis or pain in the joints, nausea, diarrhoea, constipation, vomiting, anorexia, weight loss, weight gain, skin rash, nightmares, excessive
somnolence, poor sleep, palpitations, dry mouth, other such as delayed ejaculation or anorgasmia. Complaints that were present at baseline (i.e. before the start of treatment) and that persisted at the same level of intensity during follow-up were not attributed to treatment.

Fasting blood samples were collected at 08.00 h on the day of the baseline assessment, and again after 12, 26 and 52 weeks. We used chemiluminescent microparticle immunoassay (CMIA) technology to measure tHcy on an Architect i2000SR Analyser (Abbott Ireland Diagnostics Division, Lismamuck, Longford Co., Longford, Ireland). The coefficient of variation of the assay ranges from 2.3 to 2.8%. Red cell folate and serum B12 were assayed with the Immulite 200 Xpi (Siemens Healthcare Diagnostic Ltd. Llanberis, Gwynedd) and the Architect i2000SR Analyser. Coefficients of variations were 3.5 and 4.5–8.6%, respectively.

Sample size
We based our sample size calculations on published data from a trial that used folic acid together with fluoxetine for treatment of adults aged 18 years and older with depression. They reported that 64.7% of participants treated with fluoxetine and folic acid were free of symptoms after 10 weeks compared with 48.3% of those who had been treated with fluoxetine and placebo. We calculated that a study with 310 participants (155 in each treatment arm) would have 80% power to declare such a difference between the groups as significant (α: 5%, two-tailed). We estimated that 15% of participants would have been lost by the end of week 12, and another 10% by week 52, resulting in a target sample of 388 people (194 per group). We screened 2150 people, interviewed 478 and randomised 153 (Fig. 1). The addition of two panels of data at 26 and 52 weeks was expected to circumvent the possible loss of power caused by the lower than planned number of participants recruited.

Randomisation and masking
The pharmacy of the Royal Perth Hospital carried out the independent randomisation of participants according to a list of random numbers generated by computer in random permuted blocks of 6 to 16 (1:1 allocation). Vitamins and placebo were dispensed in the form of daily capsules that had the same size, shape, colour, texture, smell and taste. Blackmores Australia manufactured all capsules. Investigators and participants remained masked to treatment assignment until all participants had completed all assessments. In addition, both investigators and study participants remained masked to the results of biochemical analyses until the final collection of end-points in September 2013.

Statistical analyses
The data were managed and analysed using the statistical software package Stata version 13.0 for Mac. We used descriptive statistics to describe the sociodemographic and clinical characteristics of participants, and Pearson’s chi-squared tests, Mann–Whitney ranked sum tests and Student’s t-tests to compare their distribution among those assigned to placebo and vitamins. Outcomes were analysed as panel data and made use of all data available at each time point. (That is, all data, including available information for participants lost to follow-up, were entered in these models and contributed to its final intention-to-treat results. In this case, no assumptions were made about missing data that could potentially bias the study findings). We used xtolstog to analyse binary outcomes such as remission of depressive episode (yes/no) (effect estimate expressed as odds ratio (OR) and respective 95% confidence intervals) and multilevel mixed-effects linear regression (xtmixed) to analyse changes of MADRS scores over time (effect estimate expressed as mean change of score). These analyses were adjusted for gender and baseline tHcy imbalances. Finally, we used contingency tables to calculate the number needed to treat (NNT) for one person to benefit from vitamin treatment, taking into account the number of participants lost to follow-up. The NNT is the reverse of the absolute risk reduction.

Results
Figure 1 shows the flow of participants from screening to analysis. The first participant entered the study on the 31 March 2009 and the last exited the study on the 11 September 2013. The age of the 153 participants ranged from 50 to 85 years and 86 of them (56.2%) were women. Table 1 shows the characteristics of participants randomly allocated to treatment with placebo and vitamins at their baseline assessment. Treatment groups were well balanced for most measured factors, except for a non-significant excess of women in the placebo group and significantly higher tHcy among those assigned vitamins. None of the participants showed evidence of low concentration of red cell folate (<260 nmol/L) or of serum vitamin B12 (<140 pmol/L).

Intention-to-treat analysis using xtolstog showed that more people treated with vitamins than placebo experienced remission over 52 weeks (OR = 2.49, 95% CI 1.12–5.51, after adjustment for gender and baseline tHcy, Table 2). The interaction between time and intervention grouping was not statistically significant. Treatment with vitamins was associated with 6.5% absolute risk reduction of major depression by 52 weeks (taking into account loss to follow-up), indicating that 16 people would require treatment for one to benefit. These calculations assumed that loss
to follow-up had occurred at random. If we assume that all participants lost to follow-up had negative outcomes (worst possible scenario), then the number needed to treat would have been 33. We also assessed the effect of treatment without adjusting for gender and baseline tHcy; the effect of treatment with vitamins was associated with a significant reduction in tHcy (−1.1 μmol/L, 95% CI −1.4 to −0.7 μmol/L; adjusted for gender and baseline tHcy), and increased red cell folate (608.4 nmol/L, 95% CI 487.8 to 729.1 nmol/L; adjusted for gender and baseline red cell folate) and serum B₁₂ (196.0 μmol/L, 95% CI 147.2 to 244.9 μmol/L; adjusted for gender and baseline serum B₁₂), indicating that treatment had the expected effect on these measures (Table 4).

We also completed post hoc analyses to ascertain whether the benefits of treatment varied according to basal tHcy. The medium basal tHcy for the sample was 10.4 μmol/L (IQR 9.1–12.3 μmol/L). Restriction of the analyses to the subgroup of 76 participants (32 placebo, 44 vitamins) with tHcy > 10.4 μmol/L confirmed that the use of vitamins was associated with greater odds of remission of symptoms over 52 weeks compared with placebo (OR = 3.47, 95% CI 1.22–9.84). Conversely, those with tHcy ≤ 10.4 μmol/L at baseline showed no evidence of benefiting from treatment with vitamins (OR = 1.09, 95% CI 0.32–3.73).

### Discussion

**Main findings**

This placebo-controlled randomised trial showed that the adjunctive use of folic acid, vitamin B₆ and vitamin B₁₂ is safe and more effective than placebo at enhancing response to treatment with placebo and vitamins. There were no differences between the study groups in any of these measures. Moreover, there were no breaches of protocol or unmasking during the study. Finally, treatment with vitamins was associated with significant reductions in tHcy (−1.1 μmol/L, 95% CI −1.4 to −0.7 μmol/L; adjusted for gender and baseline tHcy), and increased red cell folate (608.4 nmol/L, 95% CI 487.8 to 729.1 nmol/L; adjusted for gender and baseline red cell folate) and serum B₁₂ (196.0 μmol/L, 95% CI 147.2 to 244.9 μmol/L; adjusted for gender and baseline serum B₁₂), indicating that treatment had the expected effect on these measures (Table 4).

| Placebo group  
| Vitamins group  
| \( n = 76 \) | \( n = 77 \) | \( \chi^2 \) (d.f.) | \( z^b \) | t-test (d.f.) | \( P \) |
|---|---|---|---|---|---|---|
| Age, years: mean (s.d.) | 61.7 (8.2) | 63.4 (7.4) | 3.85 (3) | −1.37 (151) | 0.173 |
| Age, years, n (%) | | | | | | |
| 50–59 | 37 (48.7) | 27 (35.1) | | | |
| 60–69 | 26 (34.2) | 37 (48.0) | | | |
| 70–79 | 11 (14.5) | 12 (15.6) | | | |
| > 80 | 2 (2.6) | 1 (1.3) | | | |
| Female gender, n (%) | 48 (63.2) | 38 (49.3) | 2.96 (1) | | 0.085 |
| Migrant, n (%) | 9 (11.8) | 5 (6.5) | 1.32 (1) | | 0.251 |
| Marital status, n (%) | | | | | | |
| Single | 5 (6.6) | 6 (7.8) | | | |
| Married | 41 (53.9) | 44 (57.1) | | | |
| Separated or divorced | 25 (32.9) | 21 (27.3) | | | |
| Widowed | 5 (6.6) | 6 (7.8) | | | |
| Body mass index group, n (%)\(^c\) | | | | | | |
| Normal | 19 (25.3) | 16 (20.8) | | | |
| Overweight | 33 (44.0) | 34 (44.2) | | | |
| Obese | 23 (30.7) | 27 (33.1) | | | |
| Comorbid diagnoses, n (%) | | | | | | |
| Cardiovascular diseases | 11 (14.5) | 9 (11.7) | 0.26 (1) | | 0.609 |
| Chronic respiratory diseases | 19 (25.0) | 15 (19.5) | 0.67 (1) | | 0.412 |
| Diabetes | 8 (10.5) | 10 (13.0) | 0.22 (1) | | 0.637 |
| Hearing impairment | 16 (21.0) | 16 (20.8) | 0.00 (1) | | 0.967 |
| Past diagnosis of depression, n (%) | 58 (76.3) | 59 (77.6) | 0.04 (1) | | 0.847 |
| MMSE, median (IQR) | 29 (28–30) | 29 (28–30) | 0.345 | | 0.730 |
| MADRS, median (IQR) | 27 (22–32) | 26 (24–31) | 0.17 | | 0.865 |
| Homocysteine, μmol/L: median (IQR) | 10.3 (8.9–11.6) | 11.2 (9.3–12.9) | 2.07 | | 0.039 |
| Red cell folate, nmol/L: median (IQR) | 1268 (1057–1721) | 1352 (1002–1740) | 0.18 | | 0.851 |
| B₁₂, pmol/L: median (IQR) | 370 (300–490) | 351 (266–430) | 1.40 | | 0.163 |

**MMSE**: Mini–Mental State Examination score; **MADRS**: Montgomery–Åsberg Depression Rating Scale score.

\(a\). t-statistic derived from Mann–Whitney test adjusted for ties.

\(b\). There was missing data for one person in the placebo group.

\(c\). n = 76.

\(d\). n = 77.

\(e\). There were no breaches of protocol or unmasking during the study.

\(f\). Restriction of the analyses to the subgroup of 76 participants (32 placebo, 44 vitamins) with tHcy > 10.4 μmol/L confirmed that the use of vitamins was associated with greater odds of remission of symptoms over 52 weeks compared with placebo (OR = 3.47, 95% CI 1.22–9.84). Conversely, those with tHcy ≤ 10.4 μmol/L at baseline showed no evidence of benefiting from treatment with vitamins (OR = 1.09, 95% CI 0.32–3.73).

\(g\). This placebo-controlled randomised trial showed that the adjunctive use of folic acid, vitamin B₆ and vitamin B₁₂ is safe and more effective than placebo at enhancing response to treatment with placebo and vitamins.
antidepressant treatment over 52 weeks, but not over the initial 12 weeks. The effect of treatment with vitamins on symptom severity was not significant compared with placebo. In addition, relapse of major depression for participants who had experienced remission of symptoms by 12 weeks was less frequent among those treated with vitamins than with placebo. The beneficial effects of vitamins on mood was apparent among those in the highest 50th percentile of tHcy, but not among those in the bottom half of tHcy values.

**Strengths and limitations**

This single-site trial had a relatively small sample size and had to stop recruitment before the planned number of participants had been reached. The possible loss of power associated with decreased sample size was mitigated, in part, by the availability of repeated measures, which allowed us to analyse all available data and minimise the introduction of bias (intention-to-treat analyses). The randomisation of participants was centralised and independent of the investigators, and masking was maintained throughout the trial. The sample consisted of volunteers who consented to screening and who were subsequently diagnosed with a major depressive episode. The use of the electoral roll to approach participants living in the community might have yielded a sample that differs from samples recruited from specialised mental health services, and this might explain the relatively high proportion of participants who responded well to treatment. In addition, the outcome measures that we used in this trial to establish the presence of major depression and to monitor changes in the severity of symptoms have well-established validity. This, together with the background characteristics of our sample, gives us confidence that our results are most likely applicable and generalisable to middle-aged and older adults with major depression living in the community.

Contamination caused by the use of vitamins not prescribed by the study could represent another potential source of error in our trial, although participants were explicitly instructed not to use any other B vitamins. The consequence of such contamination would have been loss of power to declare as statistically significant differences between the groups (because some placebo-treated patients would have benefited from treatment with B vitamins). In that case, our findings could be considered conservative. However, we did have objective measures of adherence with the treatment protocol that also included blood tests. Total plasma homocysteine remained unchanged in the placebo group throughout the trial, but declined (as expected) among actively treated participants. Similarly, changes in the concentration of red cell folate and of vitamin B12 increased markedly among treated participants. However, we did have objective measures of adherence with the treatment protocol that also included blood tests. Total plasma homocysteine remained unchanged in the placebo group throughout the trial, but declined (as expected) among actively treated participants. Similarly, changes in the concentration of red cell folate and of vitamin B12 increased markedly among treated participants. However, we did have objective measures of adherence with the treatment protocol that also included blood tests. Total plasma homocysteine remained unchanged in the placebo group throughout the trial, but declined (as expected) among actively treated participants. Similarly, changes in the concentration of red cell folate and of vitamin B12 increased markedly among treated participants. However, we did have objective measures of adherence with the treatment protocol that also included blood tests. Total plasma homocysteine remained unchanged in the placebo group throughout the trial, but declined (as expected) among actively treated participants. Similarly, changes in the concentration of red cell folate and of vitamin B12 increased markedly among treated participants.

Table 2 Clinical outcomes over time of participants with major depression treated with placebo or vitamins

<table>
<thead>
<tr>
<th>n/N (%)</th>
<th>Placebo group</th>
<th>Vitamins group</th>
<th>Effect of time, b within group</th>
<th>Effect of vitamins, b between group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depressive episode in remission</td>
<td>Week 12</td>
<td>57/73 (78.1)</td>
<td>58/73 (78.4)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Week 26</td>
<td>52/68 (76.5)</td>
<td>58/68 (83.3)</td>
<td>1.16 (0.60–2.29)</td>
</tr>
<tr>
<td></td>
<td>Week 52</td>
<td>50/66 (75.8)</td>
<td>53/62 (85.5)</td>
<td>1.14 (0.57–2.26)</td>
</tr>
<tr>
<td>≥50% reduction in MADRS score</td>
<td>Week 4</td>
<td>38/74 (51.3)</td>
<td>34/73 (46.6)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Week 8</td>
<td>56/73 (76.7)</td>
<td>46/72 (63.9)</td>
<td>4.04 (2.16–7.57)</td>
</tr>
<tr>
<td></td>
<td>Week 12</td>
<td>56/73 (76.7)</td>
<td>47/73 (64.4)</td>
<td>4.07 (2.18–7.61)</td>
</tr>
<tr>
<td>Relapse after week 12</td>
<td>Week 26</td>
<td>10/57 (17.5)</td>
<td>5/58 (8.6)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Week 52</td>
<td>10/57 (17.5)</td>
<td>5/57 (8.8)</td>
<td>1.02 (0.44–2.37)</td>
</tr>
</tbody>
</table>

MADRS, Montgomery–Åsberg Depression Rating Scale score.

a. n/N: number of participants in the cell/number of participants available in the group.

b. Analyses adjusted for gender and baseline total plasma homocysteine.

c. Major depressive episode according to DSM-IV-TR criteria. Number needed to treat (NNT) for 1 person to benefit by 52 weeks is 16. If all individuals lost to follow-up were still clinically depressed, then the NNT is 33.

d. A total of 57 and 58 participants treated with placebo and vitamins, respectively, were in remission by week 12 – this subgroup was followed up to investigate relapse of symptoms at weeks 26 and 52.

e. Baseline total plasma homocysteine not included in these analyses, as relapse could only occur at or after week 26.
the absolute risk reduction associated with vitamins compared with placebo could be as low as 3%, and the NNT = 33. In this worst possible scenario, the use of vitamins would still enhance response to antidepressant treatment, but benefits would be small.

We also acknowledge that we cannot be certain about the effects of ongoing treatment with these vitamins beyond 52 weeks. Existing data suggest that extended treatment with these dosages of B vitamins is generally safe and that long-term consumption might contribute to preventing depressive episodes among those at risk. However, evidence from prolonged randomised clinical trials targeting people with or at risk of depression is not available. It is also important to note that none of our participants was B12 or folate deficient. Australia is a wealthy country where fortification of flour with folic acid is mandated and, as a result, folate deficiency is now rare. This suggests that the potential antidepressant effects of these vitamins could be more pronounced in countries where deficiency of vitamins B12 and folate is common. A similar rationale would suggest that such an intervention might be particularly relevant for adults with depression aged 75 years or older, which is the age group with the highest tHcy.

Implications
Existing observational data indicate that high tHcy and low folate increase the risk of depression and are associated with more frequent symptom relapse and treatment resistance. A
Recent trial showed that folate supplementation increases response to antidepressant treatment in adults with treatment-resistant depression, and our results now extend these findings to a community-derived unselected sample of middle-aged and older adults with major depression. In this trial, the use of vitamins B<sub>6</sub>, B<sub>12</sub> and folate did not increase the 12-week efficacy of antidepressant treatment, but enhanced and sustained antidepressant response over 1 year. Participants in the highest 50th percentile of plasma tHcy benefited the most from the use of these vitamins. Replication of these findings would mandate that treatment guidelines adopt the adjunctive use of B vitamins as a safe and inexpensive strategy to manage major depression in middle-aged and older adults.

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References


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**In a coma**

Cyrus Abbasian

The Los Angeles-based hard-rock band Guns N’ Roses released *Use Your Illusion* albums (I and II) at the height of their fame. Their lesser known but no less monstrous song *Coma*, from album I, has no chorus, is more than 10 minutes long and is in five distinct parts. It provides interesting insight about its writers, Axl Rose (lead vocalist) and Slash (lead guitarist), who struggled with mental illness and drug and alcohol misuse.

The song begins with four regular heartbeats before the bass, drums and guitars join following the heart rhythm. Throughout the song more heartbeats and beeps of an ECG machine are heard. The initial lyrics include ‘kinda like it in a coma’ and on two occasions a man yells ‘get the crash cart!’ Four minutes into the song Axl sings more blissfully; but then the drums beat rapidly, perhaps indicating ventricular tachycardia as the defibrillator is applied for the second time. Subsequent to again being ‘zapped’ the song becomes more melodramatic before turning sinister. A woman’s voice is heard talking to Axl, in the second person, mainly with a derogatory content. In the final part there is a dreaded sense of destiny with lyrics that include ‘gotta one way ticket to your suicide’.

Acute confusional state, or delirium, is not uncommon in patients who have been in comatose states. It can present with confusion and surreal fluctuating states of mind sequentially not dissimilar to the five parts of this song. These include being in and out of tranquil states, hallucinations and out of body experiences; the song makes four references to floating or sailing.

Axl Rose was diagnosed ‘manic-depressive’ and prescribed lithium. He started writing *Coma* after impulsively overdosing and being treated in hospital. Slash, in his autobiography, confesses to having used heroin, ecstasy and cocaine. He experienced drug-induced psychosis with episodes of acute paranoia, once running away naked from little versions of the aliens from the film *Predator*. Slash described the period 1999 to 2001 as his darkest, when ‘I started drinking from first thing in the morning’. He was comatose with cardiomyopathy, at one stage was given 6 weeks to live, and eventually had a defibrillator implanted.

Axl and Slash are currently well and abstinent but have not spoken for years.

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**psychiatry in music**
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