One-carbon metabolism and depression

Kim et al concluded that lower levels of folate and vitamin B12, and raised homocysteine may be risk factors for late-life depression.1 We propose to include polyunsaturated fatty acids (PUFAs) in future studies that will test the potential role of one-carbon metabolism in the aetiology and persistence of depression, for several reasons. First, because one-carbon metabolism is intimately linked with PUFA metabolism.2 The methionine–homocysteine cycle produces methyl groups for the synthesis of phosphatidylethanolamine from phosphatidylethanolamine catalysed by phosphatidylethanolamine methyltransferase. Phosphatidylcholine is critical for the delivery of important PUFAs such as docosahexaenoic acid (DHA; C22:6n-3) from the liver to the plasma and distribution to peripheral tissues. The phosphatidylcholine/phosphatidylethanolamine ratio also modulates the activity of Delta-5 and Delta-6 desaturases involved in n-3 and n-6 PUFA synthesis. Moreover, plasma homocysteine was significantly inversely correlated with DHA, total n-3 PUFA and the n-3/n-6 PUFA ratio in healthy males.3 Second, these findings are relevant for psychiatry, as PUFAs — particularly DHA and arachidonic acid — are key ‘building stones’ that are required for healthy functioning of nerve and brain cells. In patients with recurrent depression, a decrease in n-3 PUFA in erythrocyte membranes was found together with a significant positive association between the sum of plasma n-6 PUFA and homocysteine.4 There is also increasing evidence from cross-sectional studies and randomised controlled trials supporting the notion that an impaired PUFA metabolism is directly linked to the onset of depression.5,6 Third, both an impaired one-carbon and an impaired PUFA metabolism might explain the positive associations between depression and metabolic syndrome (a cluster of risk factors for cardiovascular disease). Patients with depression are at risk for all components of metabolic syndrome. Interestingly, metabolic syndrome is associated with a rise in plasma homocysteine levels and a decrease in DHA in plasma and cell membranes. Based on these findings, our opinion is that for a proper understanding of underlying mechanisms linking one-carbon metabolism and depression, homocysteine, folate and B-vitamins should be measured in conjunction with dietary and laboratory analyses of PUFAs.

Authors’ reply. As Assies & Pouwer appropriately point out, there has been growing evidence for an underlying metabolic link between the key components of one-carbon metabolism and PUFA both in depression and dementia.1 However, we do not fully agree with their recommendation for measuring these factors in combination. Our reasons are as follows. One of the main potential mood stabilising effects of PUFA in depression is thought to be their dampening action against abnormal intracellular signal transduction by (a) inhibiting G-protein-mediated actions and phospholipase-C-mediated hydrolysis of crucial membrane phospholipids;2 (b) modulating the influx of calcium ions;3 and (c) reducing the activity of protein kinase C.4 In addition, PUFA actions are closely related to inflammatory and immune pathways, which are also potentially important in the pathogenesis of depression.5 Compared with these more established findings, the evidence for relationships between one-carbon metabolism and PUFA in depression is relatively scant. For these reasons, we cannot recommend measuring PUFA in the context of one-carbon metabolism at the present time, particularly for clinical purposes. However, we do feel that Assies & Pouwer’s suggestions should encourage future animal and clinical studies on these interesting research issues.


Risk of harm after psychological intervention

In their trial of cognitive-behavioural therapy (CBT) and family intervention for relapse prevention in psychosis,1 Garety et al state: ‘There were no differences between the groups, in either [the no-carer or carer] pathway, in the primary outcomes of...’
patterns of remission and relapse. However, data in their Table 1 indicates that more patients who received CBT relapsed than those who received treatment as usual (TAU) (CBT 60/122, TAU 41/119 for all the patients randomised to CBT or TAU). A statistical analysis (logistic model) for the proportion of relapses reveals a significant reduced relapse frequency for TAU.

The differences remain significant (P=0.0153) when only patients in the no-carer pathway are considered (CBT 53/97, TAU 34/92), but there are no differences for those in the carer pathway (CBT 7/25, TAU 7/27), although here the numbers are small.

It is possible that differences in gender and age distribution between the CBT and TAU arms of the trial, or even differences between centres, could have led to different results in the statistical analyses performed by the authors. However, randomisation should have minimised such differences and the authors make no mention of them in the paper.

Hence, on the basis of the results reported, CBT appears to have a detrimental effect on relapse in non-affective psychosis.

The paper by Garety et al1 was an extremely important and methodologically robust examination of the impact of psycho-social interventions for schizophrenia. The editorial by Scott2 in the same issue suggested that there has been an overpromise of social interventions for schizophrenia. The hypothesis used to calculate power was based on the suggestion that psychological intervention might be detrimental. The data reported by Marlowe and McKenna1 suggest that this is not the case.

The published relapse rates after full remission and from full/partial remission in the no-carer pathway were 21.4% and 25.9% for TAU, 46.8% and 54.6% respectively for CBT; partial remission in the no-carer pathway were 35.4% and 37% respectively for TAU and 43.8% and 49.6% respectively for CBT; and 0.96 for family intervention. The relapse rates point towards an increase in hypothesised outcome and the risk of harm or hazard3 needs to have been discussed in greater detail, to give balance to what has already been acknowledged to be an oversold intervention.


The published relapse rates after full remission and from full/partial remission in the no-carer pathway were 35.4% and 37% respectively for TAU and 46.8% and 54.6% respectively for CBT; in the carer pathways they were 21.4% and 25.9% for TAU, 27.3% and 28% for CBT, 22.2% and 20.8% for family intervention. It would have been important to analyse the pathways separately as the no-carer pathway shows a trend for an increase in relapse rates. This was indeed the statistical evaluation in the seminal personal therapy/family therapy 3-year study by Hogarty et al,4 where offering therapeutic intervention in a no-carer pathway led to significantly increased rates of psychotic relapse. The discussion in the published paper was thus incorrect in the assertion that the effect of having a carer during psychological intervention had not been reported before.

The second table of results showed the mean number of relapses in the no-carer pathway: 0.79 for TAU and 1.17 for CBT; for the carer pathway this was 0.31 for TAU, 0.63 for CBT and 0.96 for family intervention. The relapse rates point towards an increase in hypothesised outcome and the risk of harm or hazard needs to have been discussed in greater detail, to give balance to what has already been acknowledged to be an oversold intervention.


It reported mixed findings. Our point here concerned the possibility that the hypothesis used to calculate power was based on the suggestion that psychological intervention might be detrimental. The data reported by Marlowe and McKenna1 suggest that this is not the case.

The hypothesis used to calculate power was based on full remission and from full/partial remission in the no-carer pathway were 21.4% and 25.9% for TAU, 46.8% and 54.6% respectively for CBT; partial remission in the no-carer pathway were 35.4% and 37% respectively for TAU and 43.8% and 49.6% respectively for CBT; and 0.96 for family intervention. The relapse rates point towards an increase in hypothesised outcome and the risk of harm or hazard needs to have been discussed in greater detail, to give balance to what has already been acknowledged to be an oversold intervention.


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Corrections

Efficacy of antidepressants in juvenile depression: meta-analysis. *BIP*, 193, 10–17. Page 12, Fig. 2: some minor errors (not affecting the data reported) occurred in the published version of this figure. The correct version appears below:

![Figure 2](image-url)

Community treatment orders are not a good thing. *British Journal of Psychiatry*, 193, 96–100. Page 98, col. 2: Mary O’Hagan’s name was misspelt. The relevant sentence should read: In the words of Mary O’Hagan, who initiated the service user movement in New Zealand and was the first chair of the World Network of Users and Survivors in Psychiatry, ‘community treatment orders are oppressive and corrupting – it’s tragic that other countries are following Australia and New Zealand’s example’ (M. O’Hagan, personal communication, 2007).

Computerised cognitive-behavioural therapy for depression: systematic review. *British Journal of Psychiatry*, 193, 181–184. The first sentence of the Acknowledgements (p. 183) should read: This project was funded by the NIHR Health Technology Assessment Programme (project ref. 04/01/01) and commissioned on behalf of NICE. It has been published in full in Health Technology Assessment, Vol. 10, No. 33.

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References
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