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Contents

One-carbon metabolism and depression

Kim *et al* concluded that lower levels of folate and vitamin B_{12} 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 phosphatidylcholine 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 PUFAs 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 PUFAs in erythrocyte membranes was found together with a significant positive association between the sum of plasma n-6 PUFAs 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.

1 Kim JM, Stewart R, Kim SW, Yang SJ, Shin IS, Yoon JS. Predictive value of folate, vitamin B_{12} and homocysteine levels in late-life depression. *Br J Psychiatry* 2008; **192**: 268–74.

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3 Li D, Mann NJ, Sinclair AJ. A significant inverse relationship between concentrations of plasma homocysteine and phospospholipid docosahexaenoic acid in healthy male subjects. *Lipids* 2006; **41**: 85–95.

4 Assies J, Lok A, Bockting CL, Weverling GJ, Lieverse R, Visser I, Abeling NGGM, Duran M, Schene A. Fatty acids and homocysteine levels in patients with recurrent depression: an explorative pilot study. *Prostaglandins Leukot Essent Fatty Acids* 2004; **70**: 349–56.

5 Severus WE, Litman AB, Stoll AL. Omega 3 fatty acids, homocysteine, and the increased cardiovascular mortality in major depressive disorder. *Harv Rev Psychiatry* 2001; **9**: 280–93.

6 Pouwer F, Nijpels G, Beekman AT, Dekker JM, van Dam RJ, Heine RJ, Snoek FJ. Fat food for a bad mood. Can we treat and prevent depression in type 2 diabetes by means of Omega-3 polyunsaturated fatty acids? *Diabet Med* 2005; **22**: 1465–75.

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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 PUFAs 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 PUFAs in depression is thought to be their dampening action against abnormal intracellular signal transduction by (a) inhibiting G-protein-mediated 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 PUFAs in depression is relatively scant. For these reasons, we cannot recommend measuring PUFAs in the context of one-carbon metabolism at the present time, particularly for clinical purposes. However, we do feel that Assises & Pouwer's suggestions should encourage future animal and clinical studies on these interesting research issues.

1 Das UN. Folic acid and polyunsaturated fatty acids improve cognitive function and prevent depression, dementia, and Alzheimer's disease – but how and why? *Prostaglandins Leukot Essent Fatty Acids* 2008; **78**: 11–9.

2 Sperling RI, Benincaso AI, Knoell CT, Larkin JK, Austen KF, Robinson DR. Dietary omega-3 polyunsaturated fatty acids inhibit phosphoinositide formation and chemotaxis in neutrophils. *J Clin Invest* 1993; **91**: 651–60.

3 Honen BN, Saint DA, Laver DR. Suppression of calcium sparks in rat ventricular myocytes and direct inhibition of sheep cardiac RyR channels by EPA, DHA and oleic acid. *J Membr Biol* 2003; **196**: 95–103.

4 Seung Kim HF, Weeber EJ, Sweatt JD, Stoll AL, Marangell LB. Inhibitory effects of omega-3 fatty acids on protein kinase C activity *in vitro*. *Mol Psychiatry* 2001; **6**: 246–8.

5 Maes M, Smith RS. Fatty acids, cytokines, and major depression. *Biol Psychiatry* 1998; **43**: 313–4.

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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

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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.

1 Garety PA, Fowler DG, Freeman D, Bebbington P, Dunn G, Kuipers E. Cognitive–behavioural therapy and family intervention for relapse prevention and symptom reduction in psychosis: randomised controlled trial. *Br J Psychiatry* 2008; **192**: 412–23.

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The paper by Garety *et al*[1] was an extremely important and methodologically robust examination of the impact of psychosocial interventions for schizophrenia. The editorial by Scott[2] in the same issue suggested that there has been an overpromise of CBT and the inclusion in the National Institute for Health and Clinical Excellence (NICE)[3] guideline might have been oversold as there was a lack of evidence of efficacy in schizophrenia. There are several points which need to be added to those discussed in the paper and in the editorial.

The hypothesis used to calculate power was based on the primary outcome of relapse from a non-affective psychosis (ICD–10 category F20–29, and not F2 as reported in the paper), using TAU, CBT for psychosis and family intervention as comparison interventions. It is therefore important to focus on this outcome and it is surprising that this was not analysed in greater detail.

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 analysis 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[5] needs to have been discussed in greater detail, to give balance to what has already been acknowledged to be an oversold intervention.

1 Garety PA, Fowler DG, Freeman D, Bebbington P, Dunn G, Kuipers E. Cognitive–behavioural therapy and family intervention for relapse prevention and symptom reduction in psychosis: randomised controlled trial. *Br J Psychiatry* 2008; **192**: 412–23.

2 Scott J. Cognitive–behavioural therapy for severe mental disorders: back to the future? *Br J Psychiatry* 2008; **192**: 401–3.

3 National Institute for Health and Clinical Excellence. *Schizophrenia: Core interventions in the Treatment and Management of Schizophrenia in Primary and Secondary Care*. NICE, 2003.

4 Hogarty GE, Kornblith SJ, Greenwald D, DiBarry AL, Cooley S, Ulrich RF, Carter M, Flesher S. Three years trials of personal therapy with schizophrenics living with or independent of family. I: Description of study and effects on relapse rates. *Am J Psychiatry* 1997; **154**: 1504–13.

5 Marlowe KH. Early interventions for psychosis. *Br J Psychiatry* 2005; **186**: 262–3.

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Authors' reply: Marlowe notes that the primary outcome of our trial was relapse and comments that it is surprising, therefore, that it was not analysed in more detail. McKenna *et al* attempt to analyse the relapse data further. Neither Marlowe nor McKenna *et al* appear to understand the inferential problems raised by the lack of full or partial remission in a considerable proportion of the patients in this trial. The number with full or partial remission is itself an outcome of the trial (i.e. it is a post-randomisation measure). Those who have shown no recovery are excluded from the relapse data that Marlowe and McKenna *et al* present. In fact, twice as many people show no recovery in TAU as in CBT (18:9). The data reported by Marlowe and McKenna *et al* are therefore not a causal effect of randomisation (i.e. not an intention-to-treat effect). Because of this problem, we used months in full or partial remission as our primary indicator of outcome for which a formal intention-to-treat analysis is presented. This analysis and also a further examination of total days in hospital and number of admissions very clearly demonstrate that CBT, family intervention and TAU do not differ. We also reported fully on deaths and other adverse events and found no differences (the only completed suicide was in TAU). We are therefore not at all convinced by the suggestion that psychological intervention might be detrimental. Indeed, we infer on the basis of the results of this trial and of numerous meta-analyses (e.g. Pfammatter *et al*,[1] Pilling *et al*[2] and Wykes *et al*[3]) that CBT and family intervention are beneficial for certain populations for a range of outcomes.

With respect to the point raised by Marlowe on the effects of having a carer on a psychological intervention, we are of course very aware of the Hogarty *et al* study,[4,5] which we also discuss. It reported mixed findings. Our point here concerned the apparently beneficial effect of having a carer on CBT, which has not been examined before.

1 Pfammatter M, Jungham UM, Brenner HD. Efficacy of psychological therapy in schizophrenia: conclusions from meta-analyses. *Schizophr Bull* 2006; **32** (suppl 1): s64–80.

2 Pilling S, Bebbington P, Kuipers E, Garety P, Geddes J, Orbach G, Morgan C. Psychological treatments in schizophrenia: I. Meta-analysis of family intervention and cognitive behaviour therapy. *Psychol Med* 2002; **32**: 763–82.