BJPsych | The British Journal of Psychiatry (2019) 215, 568–569.

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Edited by Kiriakos Xenitidis and Colin Campbell

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Neurometabolic approach to treatment-resistant depression

I was surprised that in the January 2019 issue of the *British Journal of Psychiatry* that was wholly devoted to treatment-resistant mood disorders there is no mention of neurometabolic investigation or treatment. Malhi *et al*, rightly emphasise our lack of understanding of pathophysiology and the future importance of identifying subtypes of depressive disorders.[1] Even in the article on augmentation therapies by Strawbridge *et al* only pharmacological and psychological treatments were considered.[2]

During the 1990s my colleagues and I identified a subgroup of patients with major depression with evidence of disturbed one-carbon metabolism reflected in low serum, red cell and cerebrospinal fluid (CSF) folate, raised plasma homocysteine and low CSF *S*-adenosylmethionine, the methyl donor in numerous vital methylation reactions in the nervous system. These findings were associated with a disturbance in monoamine metabolism i.e. low CSF 5-hydroxyindoleacetic acid, homovanillic acid and tetrahydrobiopterin through well understood mechanisms.[3] We also described significant enhancement of recovery from major depression in a placebo controlled trial of methylfolate 15 mg daily as adjunctive vitamin therapy over 3–6 months.[4]

In a further placebo controlled trial of 15 mg methylfolate for 60 days in 75 patients with selective serotonin reuptake inhibitor-resistant depression. Papakostas *et al* confirmed a significant beneficial response to this adjunctive treatment.[5] Papakostas *et al* did not describe the folate status of their patients, but a pilot study of methylfolate as monotherapy for depression suggests that any benefit is linked to improvement in folate status as measured by red cell folate.[6] In a recent review and meta-analyses of adjunctive nutraceuticals for depression, Sarris *et al* concluded that current evidence supports adjunctive use of methylfolate, *S*-adenosylmethionine, omega-3 and vitamin D.[7]

More recently Pan *et al* described a case–control neurometabolic investigation of 33 adolescent or young adults with treatment-refractory depression,[8] i.e. unresponsive to three maximum-dose and adequate duration antidepressant medication. Twelve of the patients had low CSF folate levels with normal serum folate, but red cell folate was not measured. One patient had a low CSF tetrahydrobiopterin and five patients had abnormalities of acylcarnitine profile. In an open trial of folinic acid (in addition to continuing antidepressant medication) for 6 weeks in those patients with low CSF folate all were reported to show improvement, some dramatic.

I think Malhi *et al* are right that a new approach is needed to treatment-resistant depression.[1] Academic departments of psychiatry should invest more in the neurometabolic evaluation of major depression, including in relation to responders and non-responders, and perhaps less in the continuing search for new more powerful drugs of uncertain mechanisms and undesirable side-effects. One-carbon metabolism is a potentially fertile area for such research, not least because the folate cycle is intimately linked to the synthesis of purines as well as providing the methyl groups ultimately donated by *S*-adenosylmethionine in the methylation, among others, of DNA and RNA and thus in the genetic and epigenetic mechanisms of interest to Fabbri *et al*.[9]

In the meanwhile no patient's depression need be designated treatment resistant without at least a trial of adjunctive treatment with, for example, 15 mg methylfolate for 3–6 months in conjunction with pre- and post-treatment measurements of folate and vitamin B12 status. Folic acid is an unnatural synthetic form of folate and the evidence indicates that methylfolate is a more appropriate treatment as the active and transport form of the vitamin that enters the nervous system slowly through a highly efficient blood–brain barrier mechanism.[10]

1 Malhi GS, Das P, Mannie Z, Irwin L. Treatment-resistant depression: problematic illness or a problem in our approach? *Br J Psychiatry* 2019; **214**: 1–3.

2 Strawbridge R, Carter B, Marwood L, Bandelow B, Tsapekos D, Nikolova VL, et al. Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis. *Br J Psychiatry* 2019; **214**: 42–51.

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5 Papakostas GI, Shelton RC, Zajecka JM, Etemad B, Rickels K, Clain A, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression. *Am J Psychiatry* 2012; **169**: 1267–74.

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doi:10.1192/bjp.2019.170

Authors' reply

Dr Reynolds cogently argues that a trial of methylfolate treatment should be used before using a label of treatment-resistant depression. He reminds us that he has previously identified a subgroup of patients with depression with a biochemical profile suggestive of a dysregulated one-carbon metabolism and that therefore metabolic profiling may support treatment decisions.

One-carbon metabolism refers to a complex network of biochemical reactions, including the folate cycle, which makes methyl groups and other one-carbon moieties available for cellular processes including synthesis of proteins, genomic maintenance and epigenetic methylation.[1] Folate (vitamin B9) cannot be synthesised by animals and is derived entirely from the diet, thus reduced dietary intake and impaired absorption (as can occur in coeliac disease) contribute to folate deficiency. Folate undergoes reduction to the biologically active tetrahydrofolate before entering the folate cycle.[2]

https://doi.org/10.1192/bjp.2019.171 Published online by Cambridge University Press

Methylenetetrahydrofolate reductase (MHTFR) is required in the reduction of folate. Functional polymorphisms in the *MHTFR* gene have been associated with major depressive disorder[3–5] and resistance to selective serotonin reuptake inhibitor (SSRI) treatment.[6] (10). Similarly, folate and tetrahydrofolate deficiency has been inconsistently[7] implicated in several physical, neurological and psychiatric disorders including depression[1,8] and is associated with low serotonin, dopamine and norepinephrine metabolites in the cerebrospinal fluid.[9]

Several clinical studies have been published regarding monotherapy or supplementation of antidepressants with different folate formulations. Two recent meta-analyses[10,11] incorporating a range of folate formulations did not support their use as monotherapy or augmenting agents in major depressive disorder. Restricting the analysis to just L-methylfolate was more positive.[10] This formulation is interesting because it does not require the action of MHTFR to enter the folate cycle. This analysis included only a two-phase trial by Papakostas *et al*,[12] which showed a statistically significant improvement in SSRI antidepressant effects with L-methylfolate at a dose of 15 mg and an underpowered trial by Reynolds *et al*[13] that compared amitriptyline with L-methylfolate as monotherapy.

To date, folate-related or other neuromodulatory agents have not been examined in randomised controlled trials meeting the most commonly accepted minimal clinical criteria for treatment-resistant depression (non- response to >2 treatments in the current episode) and therefore were not included in the augmentation meta-analysis conducted by Strawbridge *et al*.[14] Nevertheless, the authors are conducting a new meta-analysis using the same methods for major depression non-responsive to >1 antidepressant in the current episode (protocol registered via Prospero),[15] in which it appears likely that methylfolate, at least, may be included.

It seems therefore, that although there are some studies and a plausible rationale suggesting that folate could be clinically useful in a subgroup of patients with major depressive disorder and/or treatment-resistant depression, further work needs to be done in this area before this can become a standard recommended treatment option.

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doi:10.1192/bjp.2019.171

https://doi.org/10.1192/bjp.2019.171 Published online by Cambridge University Press