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An adjunctive antidepressant nutraceutical combination in treating major depression: Study protocol, and clinical considerations

Jerome Sarris [a,b,*], Con Stough [b], Chad Bousman [b,c,d,e], Jenifer Murphy [a], Karen Savage [a,b], Deidre J. Smith [a], Ranjit Menon [a], Suneel Chamoli [f], Georgina Oliver [a], Michael Berk [c], Gerard J. Byrne [f], Chee Ng [a], David Mischoulon [g]

[a] The University of Melbourne, Department of Psychiatry, The Melbourne Clinic, Australia
[b] Swinburne University of Technology, Centre for Human Psychopharmacology, Australia
[c] The University of Melbourne, Department of Psychiatry, Parkville, Australia
[d] Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia
[e] The University of Melbourne, Department of General Practice, Parkville, VIC, Australia
[f] The University of Queensland, Discipline of Psychiatry, Australia
[g] Depression Clinical and Research Program, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Current treatment for major depressive disorder (MDD), a prevalent and disabling mental illness, is inadequate, with two-thirds of people treated with first-line antidepressants not achieving remission. MDD is for many a chronic condition, often requiring multiple treatment attempts, thus development of additional interventions is urgently required. An emerging approach to improve non-response to antidepressants is the use of adjunctive nutraceuticals. The pathophysiology of MDD is considered to involve a range of abnormalities (monoamine impairment, neuro-endocrinological changes, reduced brain-derived neurotrophic factor, and cytokine alterations). By targeting an array of these key neurobiological pathways via specific nutraceuticals (S-adenosyl methionine; [SAMe], 5-HTP [active tryptophan], folinic acid [active folic acid], omega-3 fatty acids, and zinc), there is the potential to provide a more comprehensive therapeutic biological approach to treat depression. We are currently conducting a National Health and Medical Research Council funded study in Australia (APP1048222). The clinical trial is phase II/III, multi-site, 3-arm, 8-week, randomised, double-blind, placebo-controlled study using SAMe + folinic acid versus a combination nutraceutical (SAMe, 5-HTP, folinic acid, omega-3, and zinc) or matching placebo in 300 currently depressed participants with diagnosed MDD who are non-responsive to current antidepressants (ANZCTR, protocol number: 12613001300763). The results may provide evidence for a novel adjunctive neurobiological approach for treating depression.

1. Introduction

Major depressive disorder (MDD) is a prevalent and highly disabling mental illness, causing marked occupational and social impairment and reduced quality of life [1]. The National Health Survey conducted by the Australia Bureau of Statistics in 2001 estimated that 4.7% of Australians had taken an antidepressant medication for their mental wellbeing within the prior two weeks [2]. Further to this, depressed mood is for many a chronic condition, often requiring multiple treatment trials [3]. Complicating this, is that efficacy of established treatments are currently modest at best. This is evidenced by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, a multi-site, prospective, randomised, multi-step clinical trial comparing a series of adjunctive or alternative treatments for patients who did not respond to the selective serotonin reuptake inhibitor (SSRI) citalopram [4]. Results confirmed that only a minority of people with MDD achieve remission via initial treatment with an SSRI. Switching, combining or augmenting produced benefits to some initial non-responders, however one third of people with MDD did not achieve complete remission, even after multiple treatment strategies. Furthermore, as revealed in a highly publicised

* Corresponding author at: The Melbourne Clinic, Department of Psychiatry, The University of Melbourne, 2 Salisbury Street, Richmond, Melbourne, Australia. Tel.: +61 3 94209350.
E-mail address: jsarris@unimelb.edu.au (J. Sarris).

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2010 meta-analysis by Fournier [5], there is only a small clinical effect size between antidepressants and placebo ($d = 0.20$) in mildly ill patients. As current treatment is inadequate, development of additional interventions is urgently required. An emerging approach to improve non-response to antidepressants including SSRIs is the use of adjunctive nutraceuticals.

The pathophysiology of MDD is considered to involve a range of abnormalities such as monoamine impairment, neuro-endocrinological changes, reduced brain-derived neurotrophic factor (BDNF), and cytokine alterations (see Fig. 1) [6]. Use of adjunctive nutraceuticals may improve the clinical effect of antidepressants by addressing several key neurobiological mechanisms underpinning the disorder. These nutraceuticals include: S-adenosyl methionine (SAMe), 5-hydroxytryptophan (5-HTP), eicosapentaenoic acid (EPA), zinc, and folic acid (either folinic acid or 5-MTHF) (Fig. 2).

1.1. S-Adenosyl methionine (SAMe)

SAMe is an endogenous sulphur-containing compound that is a critical neurochemical component involved in the one-carbon cycle responsible for the methylation of neurotransmitters that regulate mood [7,8]. SAMe may improve depressed mood via enhanced methylation of catecholamines and increased serotonin turnover, reuptake inhibition of norepinephrine, enhanced dopaminergic activity, decreased prolactin secretion, and increased phosphatidylcholine conversion [9]. Animal depression models have also shown SAMe to restore the levels of putrescine in the nucleus accumbens [10]; this polyamine being shown to have antidepressant effects [11].

A recent site-based reanalysis of 144 patients from a failed 12-week 3-arm double-blind RCT [12] using SAMe monotherapy (1600 mg/day) versus SSRI escitalopram (20 mg) and placebo in adults with diagnosed MDD found a significant difference between SAMe from baseline to week 12 ($p = 0.039$) versus placebo [13]. At the week 12 endpoint, remission rates on the Hamilton Depression Rating Scale (HAM-D ≤ 7) were 34% for SAMe, 23% for escitalopram and 6% for placebo, significantly in favour of SAMe ($p = 0.014$). SAMe was found to be superior to placebo from week 1, and to escitalopram during weeks 2, 4, and 6. These results need to be interpreted with caution, however, in view of the failed parent study. In addition, a 6-week double-blind RCT by Papakostas et al. [14] involving 73 MDD patients non-responsive to SSRIs found response (HAM–D $\geq$ 50% reduction) and remission rates were significantly higher for patients treated with adjunctive SAMe (36.1% and 25.8%, respectively) than adjunctive placebo (17.6% vs. 11.7%, respectively).

1.2. 5-Hydroxytryptophan (5-HTP)

5-HTP is an essential monoamine precursor that is derived from L-tryptophan, and is required for the synthesis of serotonin [15]. 5-HTP and tryptophan have been studied as an antidepressant [16]. Eight controlled adjunctive studies using L-tryptophan or 5-HTP with antidepressants provide positive finding of augmentation effects in increasing the antidepressant response with phenelzine sulphate, clomipramine, tranylcypromine, and fluoxetine. A systematic review and meta-analysis[16] on two studies meeting criteria (pooled $n = 64$) suggest that 5-HTP and L-tryptophan monotherapy are more effective than placebo at alleviating depression (OR = 4.1, 95% CI = 1.3,13.2).

1.3. Omega-3 fatty acids

Omega-3 fatty acids have a critical role in neural function and great potential for treating depression, especially if an inflammatory causation is present [17,18]. The antidepressant activity of omega-3 fatty acids appears to occur via modulation of norepinephrine, dopamine and serotonin re-uptake, degradation, synthesis and receptor binding; anti-inflammatory effects; and the enhancement of cell membrane fluidity [19].

A meta-analysis by Martins [20] found that eicosapentaenoic acid (EPA) preparations, or those with higher EPA to docosahexaenoic acid (DHA) ratios, potentially have a stronger antidepressant effect than DHA alone. The meta-analytic comparison between DHA and EPA found that DHA monotherapy was not significant, whereas studies using supplements containing >50% EPA had a significant antidepressant effect ($p = 0.0050$). While not all monotherapy studies are supportive of omega-3 fatty acids for depression, it appears that strong evidence exists for adjunctive use with SSRIs [21]. A 12-month double-blind RCT used 460 mg EPA and 380 mg DHA in patients ($n = 2081$) with post-myocardial infarction [22]. While no effects from EPA/DHA supplementation over placebo were revealed on depressive symptoms (Beck Depression Inventory II), in a sub-sample taking conventional antidepressants, a significant antidepressant effect

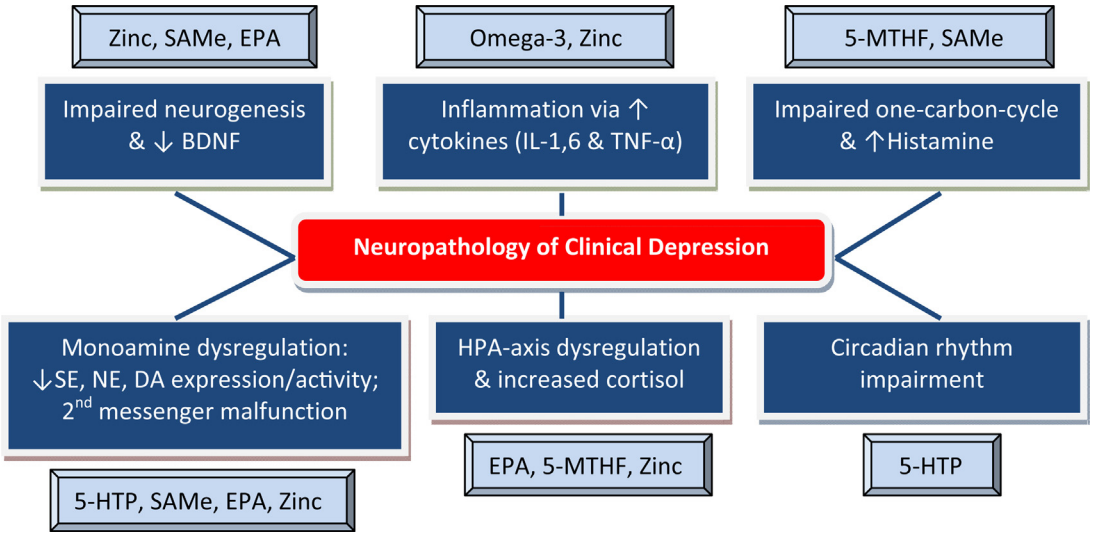

Fig. 1. Pathophysiology of depression and the nutraceuticals modulating these neurochemical pathways.