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Mitochondrial modifying nutrients in treating chronic fatigue syndrome: A 16-week open-label pilot study

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ABSTRACT

Introduction: Recent evidence suggests that mitochondrial dysfunction may play a role in the pathophysiology of chronic fatigue syndrome (CFS). We undertook a pilot investigation of a combination of nutraceutical nutrient compounds which are involved in mitochondrial function and energy generation, to assess their efficacy in improving symptoms of CFS. An open-label design was employed as CFS is largely treatment-resistant with limited placebo-response.
Methods: A 16-week open-label trial of a nutraceutical combination (primary nutrients: Coenzyme Q10, Alpha lipoic acid, Acetyl-L-carnitine, *N*-acetyl cysteine, B Vitamins, in addition to co-factors) was undertaken in ten patients with CFS. Fatigue symptoms, mood and general health were assessed at each 4-week time point over 16 weeks. Of the ten patients (7 female, 3 male) with a mean age of 36.3, eight completed the trial.
Results: Linear mixed model analysis demonstrated a significant improvement in fatigue symptoms across treatment period on the Chalder Fatigue Scale ($p < 0.001$). Specific improvements were found in tiredness, weakness, feeling sleepy or drowsy, as well as in sleep, and clinician-reported symptom-improvement. No benefit was observed in mood or other functional domains. No serious adverse events were noted.
Conclusion: These preliminary findings suggest that a combination nutraceutical compound of mitochondrial agents may improve CFS symptoms. Further investigation is warranted in a larger double-blind RCT.

1. Introduction

Chronic fatigue syndrome (CFS) is a prolonged multisystem illness, characterised by poor stamina and delayed post-exertional fatigue, that adversely affects one's functioning across numerous physical and mental domains [1]. A diagnosis of CFS is generally made only after other alternate medical and psychiatric causes of chronic fatigue have been excluded. However, uncertainty regarding lack of specific laboratory tests or markers, clear aetiology of illness, and overlap with other neuropsychiatric disorders (e.g. depression), remain barriers to effective diagnosis, treatment, and management [2]. While debate exists regarding appropriate treatment strategies, if left untreated, prognosis for recovery is generally poor [3].

It is estimated that between 2 in 1000 and 2 in 100 adults in the United States of America have CFS [4]. Current treatments for CFS include pharmacological (e.g. fluoxetine, rintatolimod and galantamine), psychological (e.g. cognitive behaviour therapy (CBT), adaptive pacing therapy), and lifestyle interventions (e.g. graded exercise) [5]. These treatments target the symptoms of CFS such as muscle pain, sleep disturbance, affective symptoms and

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fatigue [6]. A large systematic review of interventions for CFS (n = 44 studies) found mixed results for the effectiveness of most interventions [6]. The authors concluded that this is most likely due to heterogeneous study methodologies and patient populations. However, despite the methodological pitfalls, CBT and graded exercise therapy emerged as the most promising interventions for CFS currently. Although CBT and graded exercise therapy are considered to be effective treatments for CFS, the availability and access to skilled clinicians who deliver these interventions is limited, and many sufferers baulk at seeing this as a psychological problem needing a psychological approach, and many struggle with the idea of treating a disorder marked by fatigue with exercise that triggers fatigue. The attrition rates are thus high with approximately 20–40% discontinuing treatment [7]. For many who remain in treatment, they continue to experience significant social, occupational, and functional impairment. Thus new treatment approaches are urgently needed.

While fatigue remains a common complaint across numerous disorders, it is posited that CFS is related to metabolic dysfunction, oxidative and nitrosative stress [8], mitochondrial dysfunction and impaired biogenesis [1], and is in turn related to oxidative stress and systemic inflammation. Mitochondria are structures within cells primarily responsible for energy generation, and are particularly active in oxygen-rich and highly energy dependent tissues, such as the brain. Impaired energy metabolism triggers pro-apoptotic signalling (programmed cell death), oxidative damage (damage caused by free radicals), excitotoxicity (cell death due to excess cell stimulation) and impedes mitochondrial DNA repair [9]. These processes can interact and potentiate one another, which in turn results in a continuation of mitochondrial damage and subsequent energy depletion. Reduced energy levels threaten cellular homeostasis and integrity, particularly in highly metabolically active organs in the body such as the brain. Additionally, because of the high levels of oxygen metabolism in brain tissue, neural mitochondria are also highly susceptible to oxidative stress [10]. Mitochondrial dysfunction leads to further oxidative stress, which in turn causes further damage to the mitochondrion. This phenomenon of mitochondrial dysfunction has been observed in CFS, with Myhill, Booth & McLaren-Howard demonstrating a very strong correlation between dysfunctional adenosine triphosphate (ATP) metabolism and CFS [1]. As such, interventions that improve mitochondrial function, by sustaining ATP levels, have face value as being likely to improve neuronal dysfunction, and offer neuroprotection which may significantly impede the progression of neurological damage.

While research into the neurobiology and neuroimmunology of CFS has gained increasing attention of late, new therapeutic interventions remain sparse. Early research suggests that patients suffering from CFS may improve with the supplementation of mitochondrial nutrients and antioxidants [11]. Among many mitochondrial-enhancing agents to consider as potential treatments for CFS, only a selected few can be chosen for reasons of practicality. These include antioxidants (Co-enzyme Q10 [Co Q10], idebenone, *N*- acetylcysteine (NAC), vitamin C, vitamin E and menadione), agents that specifically improve lactic acidosis (dichloroacetate and dimethylglycine), agents that correct secondary biochemical deficiencies (carnitine, creatine), respiratory chain co-factors (nicotinamide, thiamine, riboflavin, pantothenic acid, pyridoxine and Co-Q10), and hormones (growth hormone and corticosteroids). This supplementation may assist in restoring mitochondrial energy production, protecting cellular structures and enzymes from oxidative damage, and decreasing fatigue. Given that CFS is largely a heterogeneous illness associated with a complex and multifactorial aetiology, it is plausible that adjunctive use of a combination of metabolic therapies may have positive effects on mitochondrial dysfunction and CFS symptoms.

2. Methods

2.1. Overview

This open-label study aimed to examine the efficacy of a novel and practical adjunctive intervention of a combination of nutraceutical agents acting on mitochondrial targets. No placebo was employed due to CFS being considered a stable chronic disorder that can be regarded as 'treatment-resistant', and with a relatively low placebo-response [12]. The original study intervention was planned to be 20-weeks, however, due to an unexpected product change from the company producing the nutraceuticals and subsequent discontinuation of the study, it was capped at 16-weeks. Thus we present the data from a 16- week open-label observational pilot study. Participants received the intervention daily, adjunctive to treatment as usual, with assessment visits at baseline, W4, W8, W12, W16. The primary outcome measure was the Chalder Fatigue Scale (CFQ). It was hypothesised that the combination therapy would improve symptoms of fatigue (assessed on the CFQ), in addition to depression, as assessed on the Montgomery-Asberg Depression Rating Scale (MADRS), and social functioning via the Health Survey and Work and Social Adjustment Scale (WSAS). All elements of this investigation aligned as closely as possible with CONSORT clinical trial criteria. Due to the open label nature of this investigation however, some CONSORT elements were not relevant and were thus not presented.

2.2. Inclusion criteria

- Males and females aged 18–65 years.
- Diagnosed with chronic fatigue syndrome by an independent physician (a letter or referral will be preferred to confirm diagnosis).
- Fulfil criteria for CFS as per the US Centres for Disease Control and Prevention (CDC), which requires persistent, unexplained fatigue for at least 6 months, concurrent with at least four of the following:
  - ○ Impaired memory/concentration.
  - ○ Sore throat, new headaches.
  - ○ Unfreshreshing sleep, muscle pain.
  - ○ Multi-joint pain.
  - ○ Tender lymph nodes.
  - ○ Post-exertional malaise.
- Have capacity to consent to the study and comply with study procedures.
- Be using effective contraception if female, sexually active and of childbearing age.
- If currently receiving treatment, stable treatment was required for at least four weeks prior to enrolment.

2.3. Exclusion criteria

- Individuals with known or suspected active and unstable systemic medical disorder.
- Individuals who have a major depressive episode in the two years preceding the diagnosis of CFS.
- Acute suicidality as indicated by a score of 5 or 6 on Item 10 of the MADRS (or at the discretion of Principal Investigator).
- Individuals with current diagnosis of a psychotic disorder, bipolar disorder, substance abuse/dependence, eating disorder, significant personality disorder.
- Recent gastrointestinal ulcers or renal stones.
- Individuals who are pregnant or lactating.
- Individuals with a diagnosis of epilepsy.

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- Those who are currently taking any of the study preparations (a 2-week washout period will be required if participants currently taking the study preparations would like to take part) or over 200 μg of selenium/day.
- Individuals currently enrolled in any other intervention study.
- Individuals needing warfarin or phenytoin.
- Individuals who are intolerant to or have had an anaphylactic reaction to any components of the preparation.
- Inability to comply with either the requirements of informed consent or the treatment protocol.

2.4. Investigational product

The trial assessed the efficacy and tolerability of twice daily dosing of a purpose-designed combination providing CFS subjects a daily amount of: ubiquinone (Co Q10) 200 mg; alpha lipoic acid 150 mg; *N*-acetylcysteine (NAC) 2000 mg; Acetyl L-carnitine (ALC) 1000 mg; magnesium (as orotate 500 mg) 64 mg; calcium ascorbate dehydrate (equiv. ascorbic acid 200 mg) 242 mg; cholecalciferol (equiv. Vitamin D3 250 IU); 12.5 ug; α-tocopherol (equiv. natural Vitamin E 50 IU) 60 IU; Retinyl palmitate (equiv. Vitamin A 3000 IU) 900 ug REIU; and vitamin B co-factors: biotin (Vitamin H) (600 ug), thiamin hydrochloride (100 mg), riboflavin (100 mg), nicotinamide (200 mg), calcium pantothenate (100 mg), pyridoxine hydrocholoride (100 mg), folic acid (800 μg), cyanocobalamin (Vitamin B12) (800 μg). All components of the active treatment are well tolerated by humans at the doses proposed for use in this study and are currently available for purchase without prescription in the USA and Australia. Nutrient dosages were established based off dosages which had been used in previous trials [13], and which had been reported to be safe and efficacious in the literature. The investigational product was provided by BioCeuticals® and manufactured according to Pharmaceutical Good Manufacturing Practice. Adherence was monitored using pill counts of returned clinical trial material.

2.5. Assessment scales

The primary outcome scale was the Chalder Fatigue Scale (CFQ) [14]. This scale is a self-report questionnaire that measures the extent and severity of fatigue. It was developed to measure the extent of fatigue in CFS but has been used as a general measure of "tiredness" across many patient populations. The Montgomery–Asberg Depression Rating Scale (MADRS), was used to assess changes in mood. It is a symptomatic questionnaire which measures severity of depression in people with a depressive disorder [15]. The use of this scale is important as sufferers of CFS may have comorbid depression, which may affect their response to treatment. The Short-Form Health Survey (SF- 12) was used to assess effects of the treatment across several health domains [16]. It a brief 12-item self-report questionnaire that measures health transition or change across four key health domains: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions. The Work and Social Adjustment Scale (WSAS) was used to assess the participant's ability to function at work, at home, management, social leisure activities, private leisure activities, and ability to maintain personal or family relationships [17].

The Clinical Global Impression Scale (CGI) is a brief clinician-rated instrument that consists of three different global measures used to assess whether the CFS was improved over time, the current severity of the condition, and the ratio of current therapeutic benefit and severity of side effects. The Patient Global Impressions (PGI) was also used to assess the patient's view of the treatment's effects. Finally, the Insomnia Severity Index (ISI) is designed as a brief screening tool for insomnia, and was used to assess the participant's sleep quality [18].

2.6. Recruitment procedure

The study recruited participants (aged 18–65 years) diagnosed with CFS by an independent physician. Subjects had not experienced a major depressive episode in two years prior to the diagnosis of CFS. Recruitment took place between May 2016 and February 2017 and was based at The Melbourne Clinic in Melbourne Australia.

Participants were administered the investigational product in an open-label fashion. Participants were primarily recruited through participants' own or private clinicians. All participants gave written informed consent before enrolment. Once a participant was approached to participate in this research they were given a copy of the Participant Information and Consent Form to review. Participants were initially required to attend assessment visits at baseline, W4, W8, W12, W16, and W20 (although the study was altered to a 16-week study during the course of the project). Assessments as detailed above were conducted at every time point.

Dose changes to existing medications (either increases or decreases in dose), or addition or removal of agents were accepted and participants were allowed to continue with the trial. Psychosocial interventions (i.e. CBT or graded exercise therapy) were monitored throughout trial participation.

2.7. Data analysis

No formal sample size calculation was performed as the study is open-label and exploratory in nature. The sample size will be a sample of convenience as there was limited funds for advertising and was reliant on the Principal Investigator's access to patients with CFS. Data analysis was conducted using SPSS version 23 (IBM). Analysis of all outcome measures was performed at each time point from week 0 to week 16. Repeated measures linear mixed effects models were used to test the effect of the intervention on primary and secondary outcome measures over time. In each instance, visual inspection of the data, as well as Schwarz's Bayesian Criterion (BIC), were used to determine the appropriate covariance structure. Early withdrawals and missing data was dealt with using an intent-to-treat analysis model in which all available data was analysed. All analyses adopted $\propto = 0.05$ as a point of significance.

3. Results

3.1. Participant characteristics

Ten patients with Chronic Fatigue Syndrome were enrolled in the study with an average illness duration of 11 years (SD = 7.04 years). Over half the participants were female ($n = 7$; 70%) and the sample had an average age of 36.30 years (SD = 10.46 years). Half the sample were not currently working due to their illness ($n = 5$; 50%). Sociodemographic details, as well current medications are summarised in Table 1. Two participants (20%) withdrew from the study before termination, at week four and week twelve, in both cases due to work commitments.

3.2. Fatigue, physical and mental health outcomes

As displayed in Fig. 1 and Table 2, a significant reduction occurred for mean total CFQ scores across Time from baseline to

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Table 1
Demographic Information for Chronic Fatigue Patients Receiving Intervention.

	Sex	Age	Employment Status	Education	Length of CFS Illness (years)	Concurrent Medications (daily dose)
1	M	47	Unemployed	Trade	5	Nil
2	F	44	Unemployed	Tertiary	4	Moclobemide (300 mg)
3	F	42	Unemployed	Trade	12	Tetracycline (300 mg); Agomelatine (25 mg); Rizatriptan (dose unknown)
4	F	18	Unemployed	Highschool	10	Pregabalin (600 mg); Celecoxib (400 mg); Acetaminophen (3375 mg); Duloxetine (60 mg); Nitrazepam (15 mg); Methylphenidate (40 mg)
5	F	34	Full time	Tertiary	26	Escitalopram (5 mg)
6	F	47	Unemployed	Trade	5	Citalopram (40 mg); Tamoxifen (20 mg)
7	F	43	Full time	Trade	13	Nil
8	M	35	Part time/Cas-ual	Tertiary	14	Pregabalin (150 mg); Tramadol (100 mg)
9	F	33	Full time	Trade	17	Moclobemide (300 mg)
10	M	20	Student	Highschool	4	Escitalopram (20 mg); Quetiapine (12.5 mg)

Week 16, ($F(4,29) = 6.31$ $p < 0.001$). Across the time points, the most notable reduction was observed between baseline and Week 4, mean difference 7.66, $p < 0.01$. Of the 11 items within the CFQ, nine showed significant improvement (Fig. 2). Need for more rest, item 2, revealed the most striking improvement over Time with a 55% improvement in symptom severity ($F(4,33) = 3.97$, $p < 0.01$). The other items which showed improvement were time spent resting, tiredness, energy levels, strength, weakness, concentration, slips of the tongue, and difficulties finding the right word. The two items which showed no significant improvement were memory, item 11, and problems starting things, item 4.

Significant improvement was also noted in the ISI, as well as the CGI-I scale, over the 16- weeks, $F(4,32) = 3.55$, $p = 0.017$ and $F(3,24)$, $p = 0.014$, respectively. No significant changes over time was noted in total MADRS score, $F(4,32) = 1.50$, $p = 0.225$; PGI, $F(3,22) = 1.62$ $p = 0.33$; CGI- S, $F(4,33) = 1.81$ $p = 0.150$; WSAS, $F(4,26) = 2.21$, $p = 0.095$, or any of the individual measures of the SF-12.

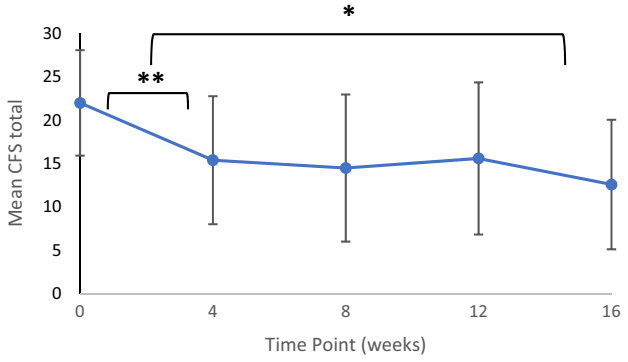

Fig. 1. CFS Total from Baseline (week 0) to Week 16.
Error bars indicate 1SD from the mean; *significant difference ($p < 0.001$) across time; ** Significant difference ($p < 0.01$) from baseline to Week 4.

3.3. Safety assessment

The most common adverse events observed were headaches/migraines (n = 3), minor gastritis (n = 4), loss of appetite/feeling of fullness (n = 1), brief tachycardia (n = 1) and notable skin pigmentation on the forehead (n = 1). No participants withdrew from the study due to adverse events.

4. Discussion

This open label adjunctive trial of a combination nutraceutical therapy in CFS yielded some positive findings. Severity of chronic fatigue symptoms appeared to improve across the trial, as measured by the CFQ and clinical reported improvement score (CGI-I). Further, insomnia symptoms also appeared to improve. There was no significant change on the MADRS, PGI, CGI-S, WSAS or any of the individual measures of the SF-12. Overall, the intervention appeared to be well tolerated with no serious adverse events. One comparable study ($n = 15$) utilising a combination therapy of mitochondrial agents (including many of the same agents used in this study) in conjunction with a stimulant drug, demonstrated similar results [19]. However, when expanded into a larger double-blind controlled trial ($n = 128$), the intervention failed to significantly outperform placebo on the primary outcome (Unpublished – Synergy trial, 2015). Thus, our results demonstrated here should be considered in light of this more rigorous study.

Table 2
Primary and Secondary Outcomes from Baseline to Week 16.

Outcome	Baseline	Week 4	Week 8	Week 12	Week 16	Test Statistic	
CFQ	22.0 (6.07)	15.4 (7.37)	14.5 (8.47)	15.6 (8.76)	12.6 (7.46)	$F(4,29) = 6.31$	$p < 0.001$
MADRS	7.70 (6.31)	10.2 (6.25)	12.8 (8.44)	9.67 (5.07)	10.3 (7.29)	$F(4,32) = 1.50$	$p = 0.225$
ISI	12.3 (5.81)	11.4 (5.95)	10.0 (4.61)	9.89 (5.95)	7.75 (4.68)	$F(4,32) = 3.55$	$p = 0.017$
PGI	–	3.60 (0.843)	3.38 (0.916)	3.00 (5.35)	3.13 (0.991)	$F(3,22) = 1.62$	$p = 0.213$
CGI-S	4.50 (0.527)	4.20 (0.421)	4.22 (0.667)	4.00 (0.500)	4.25 (0.707)	$F(4,33) = 1.81$	$p = 0.150$
CGI-I	–	3.80 (0.632)	3.33 (0.707)	3.32 (0.441)	2.88 (0.835)	$F(3,24) = 4.35$	$p = 0.014$
WSAS	24.9 (8.65)	24.4 (7.91)	21.6 (8.63)	22.8 (8.33)	23.0 (8.31)	$F(4,26) = 2.21$	$p = 0.095$

CFQ = Chalder Fatigue Scale; MADRS = Montgomery-Asberg Depression Rating Scale; ISI = Insomnia Severity Index; PGI = Patient Global Impressions; CGI-I = Clinical Global Impressions- Improvement; CGI-S = Clinical Global Impressions-Severity; WSAS = Work and Social Adjustment Scale.

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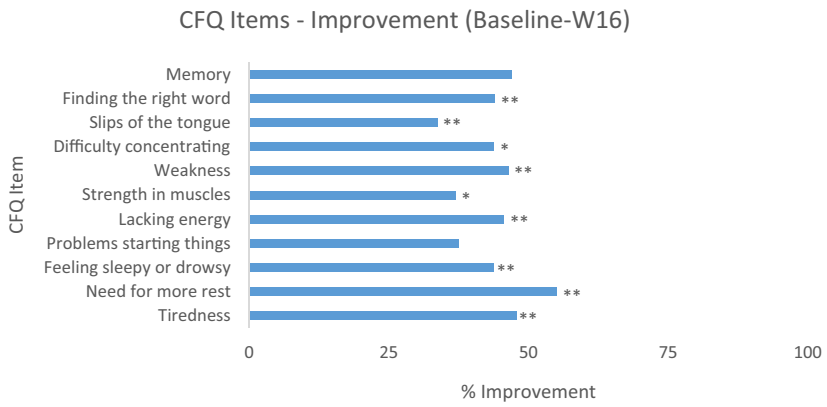

Fig. 2. Mean percent (%) improvement in each item of the Chalder Fatigue Scale (CFQ; from baseline to Week 16); *Significant difference ($p < 0.05$); **Significant difference $p < 0.01$.

A notable limitation of this study was the variation in type and quantity of concomitant medications between participants. In particular, it is difficult to discern whether adverse events may have been a consequence of the nutraceutical treatment or otherwise due to concomitant medications. Similarly, concomitant medications may have been a confounder as further benefit may have been limited or otherwise masked, particularly in the patients taking multiple medications. Future studies should aim for greater consistency in concomitant medications between patients in order to more conclusively evaluate efficacy, safety and side effects.

The preliminary results of this study must be interpreted with caution due to both the small sample size and open-label design. However, despite this caveat, the findings provide tentative support for the efficacy of the intervention (especially in the context of improved energy beyond the participant's treatment as usual, and relative treatment-resistance). For example, we found that the most significant benefit was observed within fatigue symptoms (CFQ), the item 'tiredness' in particular, as opposed to other measures less directly related to CFS symptomology. This provides some support for the improvement demonstrated being due to the intervention rather than a 'participation effect', as improvements were largely localised to where the intervention was hypothesised to have most benefit, rather than across all clinical measures. Further, results from the PGI suggested that patients did not appear to be aware of any improvement in CFS symptoms, despite clinical measures demonstrating some improvement, which suggests that benefit may not have been related to a conscious participation effect.

The time course of the intervention in the study needs to be noted. Most of the clinical improvement was observed within the first four-weeks, and aside from a slight increase of benefit from W12 to W16, appeared to plateau somewhat following this. Thus it is possible that the benefits of the intervention may have a ceiling effect. As the trial was terminated at week 16, it remains to be seen how response may change over a longer time course.

Overall, this open label trial of a nutraceutical combination in CFS demonstrated some positive preliminary results. Due to small sample size and lack of placebo control, results should be interpreted with caution. Despite this, observed improvement in fatigue symptoms suggest that combination therapies of nutraceutical mitochondrial agents are safe, tolerable and promising potential treatments in CFS.

Author's contributions

JS and LC drafted the initial version of this manuscript. All authors contributed intellectual content to the manuscript and read and approved the final manuscript.

Conflicts of interest

RM has received presentation honoraria from Astra Zeneca, Servier and Lundbeck. JS has received either presentation honoraria, travel support, clinical trial grants, book royalties from Integria Healthcare & MediHerb, Pfizer, Taki Mai, Bioceuticals & Blackmores, Soho- Flordis, Healthworld, HealthEd, HealthMasters, Elsevier, Chaminade University, International Society for Affective Disorders, Complementary Medicines Australia, Terry White Chemist, ANS, Society for Medicinal Plant and Natural Product Research, Omega-3 Centre, the National Health and Medical Research Council, CR Roper Fellowship. MB has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, MBF, NHMRC, Beyond Blue, Rotary Health, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Meat and Livestock Board, Organon, Novartis, Mayne Pharma, Servier, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Merck, Pfizer, Sanofi Synthelabo, Servier, Solvay and Wyeth, and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Eli Lilly, Grunbiotics, Glaxo SmithKline, Janssen Cilag, LivaNova, Lundbeck, Merck, Mylan, Pfizer and Servier. Served the Janssen, Servier, Wyeth and Eli Lilly Advisory Boards, received research grant support from Wyeth and Lundbeck and speaker honoraria from Bristol-Myers Squibb, Organon, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Astra-Zenaca, Wyeth, Pfizer and Servier. MA has received grant/research support from Deakin University, Australasian Society for Bipolar Depressive Disorders, Lundbeck, Australian Rotary Health, Ian Parker Bipolar Research Fund and Cooperative Research Centre for Mental Health.

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