Inflammopharmacol
DOI 10.1007/s10787-017-0311-x

Inflammopharmacology

SHORT COMMUNICATION

A combination of probiotics and magnesium orotate attenuate depression in a small SSRI resistant cohort: an intestinal anti-inflammatory response is suggested

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Received: 28 December 2016 / Accepted: 16 January 2017

Abstract Approximately, one-third of those who develop major depression will have a poor response to treatment and over time can become treatment resistant. Intestinal dysbiosis has been implicated in depression with systemic inflammation and vagal and enteric nerve impairment. We report on a sequel pilot study ($n = 12$) with a combination probiotics/magnesium orotate formulation adjuvant administered with SSRIs for treatment resistant depression. At the end of an 8-week intervention mean changes for depression scores and quality of life in the group was clinically significantly improved ($p < 0.001$) with all but 4 participants experiencing a benefit. An intestinal anti-inflammatory response was suggested. At 16-weeks follow-up while still on SSRI medications, the group had relapsed after cessation of the test intervention.

Keywords Depression · SSRI · Treatment resistance · Probiotics · Intestinal dysbiosis · Inflammation · Magnesium orotate

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Introduction

Depression is a common presenting problem in both primary and specialist health care settings (WHO 2012). Treatment non-responders tend to remain depressed whilst on medications, and with repeated episodes over time, may be considered treatment resistant. This group may benefit from emerging evidence that suggests that an important mechanism for depression treatment non-response may be targeting intestinal dysbiosis (a gut epithelial barrier abnormality) mediated systemic inflammation (Vitetta et al. 2014; Bambling et al. 2015). The intestinal microbiota is established as essential for correct peripheral and central nervous system communication via the vagal system and is strongly implicated in mood disorders among other health conditions, such as immune-dysregulation (Bested et al. 2013). The intestinal microbiome is especially sensitive to host emotional states and environmental factors. In animal models, dysbiosis has been demonstrated to impair vagus signalling which results in reduced protein synthesis in the hippocampus, corrected by rescuing the intestinal mirobiome with either specific strains of probiotics or a more gradual recovery with the removal of the stressor(s) (Dinan and Cryan 2013; Fond et al. 2015). A recent review synopsizes animal models that suggest that the intestinal microbiota has a central role in the genesis of the HPA axis (Fond et al. 2015). Furthermore, that the serotoninergic system, the immuno-inflammatory system, and the indigenous intestinal microbes can affect the CNS through multiple pathways (Yano et al. 2015; Fond et al. 2015). Specific strains of probiotics have been shown to improve anxiety as well as repair intestinal dysbiosis in animal models and some human studies have provided encouraging results for improving mood and anxiety (Vitetta et al. 2014; Yano et al. 2015; Sharon et al. 2016).

Published online: 02 February 2017

Methods

The study was approved by the University of Queensland human research ethics committee Approval Number: 2012000647; and was registered with the Australian and New Zealand Clinical Trial Registry Number: ACTRN12614000544673.

Study design

Single group allocation intervention and follow-up study with prescribed SSRI medication, that associates with our previous pilot work (Bambling et al. 2015). The probiotics/magnesium orotate active intervention was administered for 8-week. Participants completed a diagnostic DSM-ICD assessment at enrolment/baseline using Beck Depression Inventory (BDI), Outcome Questionnaire 45 (OQ45) and Quality of Life (QoL). At 16-week follow-up (8-week post treatment completion) all measures were readministered. Participants were contacted weekly to ensure well-being and study conformity, and completed a dosage log-book, which confirmed a high degree of conformity to the study protocol.

Participants

Participants were recruited on a rolling allocation basis. Seventeen participants were assessed as eligible from a pool of 36 inquiries meeting the criteria for resistant depression being currently depressed while on antidepressant medication with a history of multiple depressive episodes with poor treatment response. The average years participants experienced depression was $n = 19.8$, SD = 5.7. Table 1 presents subject demographics and established history of treatment resistance. The test intervention consisted of capsules administered pre meals as a combination of lyophilized probiotics (*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Streptoccocus thermophiles* total CFU of 2×10^{10}) and magnesium orotate 1600 mg divided in two daily doses.

Measures

Mini International Neuropsychiatric Interview (MINI. 5) served as the primary clinician diagnostic tool with high validation and reliability scores (Sheehan et al. 1998). BDI widely used to assess depression with high internal constancy and correlates highly with other self-report measures of depression (Wang and Gorenstein 2013). OQ45 is a self-report symptom and distress inventory and designed as an independent measure of symptom distress and functioning to assess the response to intervention and is suitable both as a diagnostic measure as well as treatment response measure that can plot clinical change over treatment. A high total score >80 is indicative of a high level of symptom distress (anxiety, depression, somatic, work and social role problems; Vermeersch et al. 2000) Average community non-clinical scores cut-off occur at <63 and changes of 14 points in either direction are considered clinically significant changes and deemed research reliable. QoL evaluates perceived satisfaction with life over a number of domains and provides an important evaluation of perception of life circumstances and stressors (Burckhardt et al. 1989). There were strict entry criteria with thorough precondition assessment applied, to ensure that the

Table 1 Probiotics-magnesium orotate combination treatment

	N	Week 1		Week 8 endpoint			Week 16 follow-up			*Units of clinical change (UCC) at 8-weeks
		Mean	SD	Mean	SD	*p* value	Mean	SD	*p* value	
BDI	12	30.2	3.7	16.1	15.8	0.005	23.5	7.1	0.068	2.8
OQ45	12	99.2	14.6	65.6	15.9	0.000	93.8	12.2	0.000	2.4
QOL	12	57.5	8.5	70	19.1	0.052	56.7	7.4	0.052	1.8
Treatment non-responders										
BDI	4	33.5	2	28.5	22.5					1
OQ45	4	117.5	2.6	81.2	16.1					2.5
QOL	4	56.5	6.3	54.5	25.9					0

	Mean	SD
Mean age	49.3	10.9
Years of MDD	19.8	5.7
Gender: female ($n = 8$) male ($n = 4$)		

* UCC = BDI 5 points, OQ45 14 points, QOL 7 points

participants had a proven history of treatment non-response.

Statistical analysis

All data tested to ensure it met assumptions for normal distribution using the Shapiro–Wilk test and there was no missing data. Data analysis consisted of a repeated measures *t* test conducted on SPSS version 22. Intervals of assessment included pre, endpoint and follow-up for the BDI and QoL, and pre, weekly, and follow-up for the OQ45.

Results

The most common comorbid condition was anxiety 60% and $n = 7$ participants also met the criteria for a personality disorder. Three participants dropped out of the study for undetermined reasons as they remained un-contactable and 2 participants did not return their data despite repeated follow-up contact. Twelve participants completed the study with no missing data with high conformity to the dosage protocol.

BDI scores (Table 1) demonstrated a significant decrease indicating mild depression from baseline by 8-week $p = 0.005$ and a trend to relapse by follow-up $p = 0.068$. While the relapse trend was not statistically significant it was clinically significant indicating major depression in the participant group. OQ45 scores demonstrated a significant decrease (Fig. 1) from baseline approaching remission to study endpoint $p = 0.001$ and significant increase in scores by follow-up $p = 0.000$. Borderline insignificant QoL scores demonstrated an increase from baseline to study endpoint $p = 0.052$ and decrease in scores by follow-up $p = 0.052$ (Fig. 2). Four sub-optimal responders (Table 1) experienced significant clinical change on the OQ45 = 2.5 U, however, they were not in remission by treatment endpoint and remained clinically distressed. This group experienced 1 U of clinical change on the BDI and moved from major depression severe to major depression moderate.

Discussion

We report on the overall beneficial response to a combination of probiotics/magnesium orotate in subjects diagnosed with SSRI treatment resistant depression. The results demonstrated a mean BDI score at treatment endpoint of 16.1 (mild depression). An OQ45 score of 65.6 that approached the clinical cut-off score of 63 (considered non-clinical). The participants who responded to treatment reported a subjective increase in well-being and improved energy levels. Four participants that recorded a minimal change over the course of treatment could not be considered to have benefited significantly from the intervention.

Limitations of this study included the inability to determine if the addition of probiotics achieved preferable outcomes compared to magnesium orotate alone and the lack of a control group merits caution when interpreting the data. Notwithstanding, the results of this pilot study support our previous work with magnesium orotate (Bambling et al. 2015) that adds validity to the current findings. Hence, it is reasonable to posit that there may be a treatment signal for the combined use of magnesium

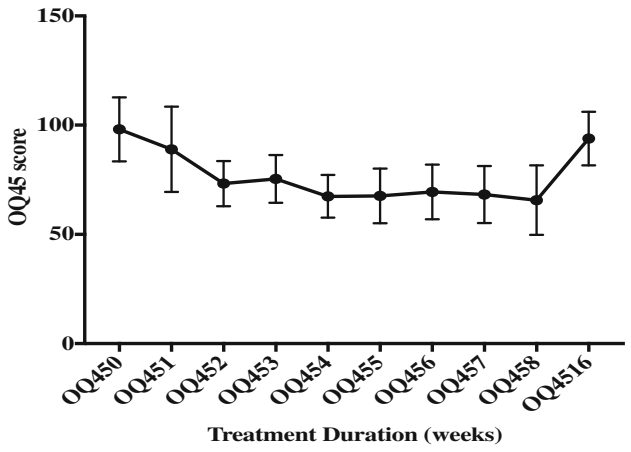

Fig. 1 Symptom response from baseline to 8-weeks (OQ450–OQ458) following the oral administration of 1600 mg of magnesium orotate and 10 billion CFU *L. acidophilus*/4 billion CFU *B. bifidum*/6 billion CFU *S. thermophiles*. Treatment ceased at week 8 and follow-up at 16-weeks (OQ4516)

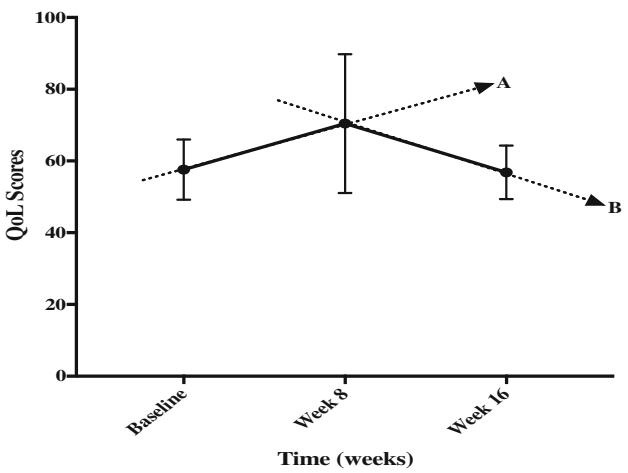

Fig. 2 Changes in quality of life (QoL) experienced from baseline to 8-week at end of study improvement (**a**) and follow-up at 16-weeks with a QoL scores return to baseline (**b**)

orotate + probiotics, which justifies continued investigation as an adjuvant treatment approach.

Mechanistically the importance displayed by the gut–brain axis has been suggested to be in the provision of a bidirectional flow of neuroendocrine and neuroimmunological control of end-organ (i.e., the brain) functionality by eliciting critical homeostatic control (Dinan and Cryan 2013; Yano et al. 2015). Indirect measurements have made linking immuno-endocrine modulation to intestinal dysbiosis and then depression contentious (Dinan and Cryan 2013; Furness et al. 2013; Maes et al. 2013). Depression linked to antagonistic immuno-endocrine control of homeostasis may be an *inside* (*intestinal mucosa*) *to outside* (*intestinal lumen*) problem (Vitetta et al. 2014) that is exacerbated by intestinal microbiome adverse shifts that maintain low-level pro-inflammatory activity and intestinal dysbiosis.

We further posit that the administration of probiotics and magnesium orotate may have contributed a significant anti-depressive effect. The decrease in functional distress by treatment responders suggests a link between attenuation of intestinal dysbiosis to improvement in depression that is worthy of further investigation.

Acknowledgements Luis Vitetta has received National Institute of Complementary Medicine and National Health and Medical Research Council of Australia competitive funding and Industry support for research into nutraceuticals and probiotics. In addition, Luis Vitetta and Sean Hall are involved in research with probiotics at Medlab Clinical. Medlab Clinical provided seed funding and the investigational product (NRGBiotic) (containing specific probiotic species and Magnesium Orotate and specific laboratory testing of the product).

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