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S-adenosylmethionine (SAMe) and Magnesium Orotate as adjunctives to SSRIs in sub-optimal treatment response of depression in adults: A pilot study

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ABSTRACT

Major depression is a prevalent mental health disorder and a proportion of patients do not respond adequately to standard treatment. The use of nutraceutical adjunctives with antidepressant medication such as high dose S-adenosylmethionine (SAMe) has proven beneficial in terms of initial symptom response but the effect on symptom maintenance and relapse is unknown. In this pilot study [$n = 36$], participants [26 evaluable subjects] with established sub-optimal response to treatment for major depressive disorder and who were prescribed Selective Serotonin Reuptake Inhibitor (SSRI) medication were randomly allocated to either 1600 mg or 800 mg daily of SAMe for 15 weeks duration to evaluate the efficacy on both symptom response and maintenance. A variety of validated psychiatric measures of symptoms and mood including clinician assessment and self-report measures were used to assess outcome measures. Both SAMe doses achieved similar results with a significant proportion of participants (35%) achieving significant symptom improvement at the end of 15 weeks supplementation as assessed by the Beck Depression Inventory (BDI), Outcome Questionnaire 45 (OQ45), and improved Quality of Life (QOL) scores. After a 2 week washout period, SAMe non-responders were then supplemented with 1600 mg of Magnesium Orotate for 8 weeks duration which resulted in significant clinical improvement as measured by BDI, OQ45 and QOL scores [$n = 8$]. We progress the SAMe-methylation and Orotate–uridine hypothesis and consider that the response to these novel compounds implicates the microbiome as an important agent for the adjunctive treatment of sub-optimal response to pharmaceutical medications.

1. Introduction

Depression is a prevalent mental illness with the burden of care second only to heart disease [1]. Lifetime prevalence rates for depression in the Australian community have been estimated at 25% for females and 12% for males [1]. Antidepressant medication treatment assists with at least 30% of acute episodes and one third of patients treated for depression relapse within a year [2,3]. Those who have experienced two episodes have a 90% chance of experiencing a third [2,3] with 40% relapsing within 15 weeks [4]. Such patients are considered to have a sub-optimal response to current pharmacological treatments [5–11]. No single class of antidepressant medication is implicated in poor treatment response [11]. Patients with a history of sub-optimal response often demonstrate a poor response to different classes of antidepressants or combinations of medications [11].

Pharmacotherapy achieves acceptable results for about 30% of patients, mixed results for 40% and poor results for 30% of patients [10]. As a result of poor or variable response to treatment, a significant proportion of depressed patients may not experience complete clinical remission of their depression [11]. Treatment response is complicated further by poor patient tolerability of medications due to unwanted side effects [10,11]. Furthermore, patients with suboptimal treatment response often present with a variety of comorbid health problems such as endocrine and lipid disorders and gastrointestinal (GIT) dysfunction (dysbiosis). This suggests that complex physiological mechanisms maybe involved

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with depression development and treatment response [12]. Hence novel approaches to enhance treatment response without increasing side effects are warranted.

S-adenosylmethionine (SAMe) has been available as a nutritional supplement in Australia since the late 1990s. It is a naturally occurring compound synthesised from methionine within the human body and is essential for numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and neurotransmitters. SAMe has a variety of pharmacological effects in the central nervous system (CNS), specifically in monoamine neurotransmitter metabolism and receptor systems [13]. SAMe produces therapeutic effects similar to several classes of commonly used antidepressants and is well tolerated at high doses [14,15]. Anti-depressants typically inhibit the reuptake of neurotransmitters (e.g. serotonin), while SAMe's role as a methylating compound enhances endogenous synthesis of neurotransmitters involved with mood such as serotonin, norepinephrine and monoamines. Hence from a safety perspective SAMe can be used with existing antidepressant medications that only target neurotransmitter reuptake [13]. While there are over 40 clinical trials assessing the efficacy of SAMe for depression with dosage ranging from 400 to 1600 mg daily, only three of these used rigorous empirical designs albeit with very small sample sizes. Further, only five studies used oral doses of SAMe. These studies also had methodological problems regarding baseline data and clinical response calculations [16–18].

A recent study investigated the impact of SAMe co-administered with Selective Serotonin Reuptake Inhibitors (SSRI) medication in sub-optimal treatment response patients [19]. Seventy-three SSRI non-responders were provided with either 1600 mg of SAMe per day or a placebo in a randomised trial for 6 weeks duration. The high dose SAMe proved efficacious with 36% of the supplemented group experiencing significant clinical symptom improvement of which 26% experienced remission. The control group achieved 12% response compared to the SAMe condition. This short duration study used the Beck Depression Inventory (BDI) as the primary baseline and outcome measure. The issue of differential dosage and symptom maintenance over time was not examined. The study demonstrated that SAMe was an effective adjunctive for a significant proportion of patients who had a sub-optimal response to SSRI medication. Further investigation is warranted into SAMe regarding optimal dosage and symptom maintenance [19].

Uridine is a pyrimidine nucleoside containing uracil attached to a ribose ring and is essential for the synthesis of RNA, DNA and biomembranes as well as glycogen and protein turnover [20]. Uridine is associated with the regulation of the peripheral and central nervous systems influencing neuronal signalling, mitochondrial function, fatty acid synthesis, synaptic formation, protein and glycogen metabolism, that may affect the metabolic function of the brain. Uridine further provides a substrate in phosphatidylcholine (PC) synthesis [20–22]. It is understood that the mechanism of uridine in treating depression is via the cytidine 5′-diphosphocholine pathway which provides a critical substrate for phospholipid synthesis [23]. Primary research associated with uridine has demonstrated encouraging results as a possible antidepressant agent in analogue models with mice and also in improving symptoms of bipolar (depressive cycle) in children [21]. Uridine has also been shown to improve hippocampal metabolism and possibly raise dopamine levels [21,23]. While considered safe, uridine is both a complex and an expensive molecule for use in research.

Orotate, also referred to as orotic acid, is available as a salt complexed with magnesium, calcium, potassium or zinc ions [24]. It is safe and inexpensive and rapidly increases uridine synthesis in a dose dependent manner [24]. Orotate phosphoribosyl transferase and orotidine-5′-decarboxylase are enzymes responsible for catalysing the formation of uridine monophosphate (UMP) [24]. Orotic acid is nearly structurally identical to uracil and is efficiently taken up by cells via the uracil transporter. Orotic acid participates in numerous cellular metabolic activities such as RNA and DNA synthesis and altering cell metabolism for example by increasing carnosine levels, mediating inflammatory processes and increasing cerebral blood flow. The implications for depression however are unknown. Magnesium facilitates the absorption and conversion of Orotate and represents a cost effective and readily available standardised product that is suitable for research applications in modulating uridine metabolism [21,23].

The aims of this study were to conduct a pilot examination of the efficacy of high dose SAMe (1600 mg) used in previous adjunctive research [19] compared to a lower dose (800 mg) on depressive symptom maintenance and relapse (Table 1). To assess the impact on symptom maintenance, 15 weeks was chosen as representing the earliest interval that a significant proportion of relapse would be expected to occur [4]. As a pilot investigation without a placebo control, validity was improved by using a variety of psychiatric measures for diagnosis, symptom validation and symptom tracking. Further, we corrected for potential placebo effect with a control statistic calculated from the control condition in a similar previous study [19].

After conducting the SAMe trial we identified sub-optimal treatment responders to the SAMe plus SSRI protocol and then inducted them into a separate 8 week trial of Orotate plus SSRI. The advantage of inducting SAMe non-responders was to further control the likelihood that any treatment response noted was the result of the Orotate intervention (Fig. 1).

The investigation was guided by two hypotheses:

1. The administration of a high daily dose of SAMe (1600 mg per day) would produce statistically significant improvements in

Table 1
Participant health problems by condition ($n = 36$).

	Group 1: 1600 mg SAMe ($n = 18$) *N*	Group 2: 800 mg SAMe ($n = 18$) *N*
Health problems		
Hyperlipid	2	3
Head injury	1	1
Chronic pain	1	0
Endocrine	5	4
Autoimmune	4	3
Obesity	3	4
Cardiovascular	2	3
Note: patient health condition listed by their most serious problem. Many patients had secondary health concerns in addition to their most serious problem.		
History of trauma		
Sexual abuse	4	3
Physical abuse	3	3
Emotional abuse	2	3
Family conflict	3	3
Neglect	4	3
Traumatic loss	3	2
Note: patient history of trauma listed by their most serious concern. Many patients had secondary experiences of abuse, trauma and loss in addition to their most serious concern.		
Primary and secondary diagnosis		
MDD only	1	1
MDD + AD	9	10
MDD + PTSD	0	2
MDD + Grief	1	0
MDD + PD	3	3
Note: MDD, major depression severe; AD, one of the anxiety based disorders; PTSD, Post-Traumatic Stress Disorder; Grief, protracted grief reaction; PD, one of the personality disorders.		

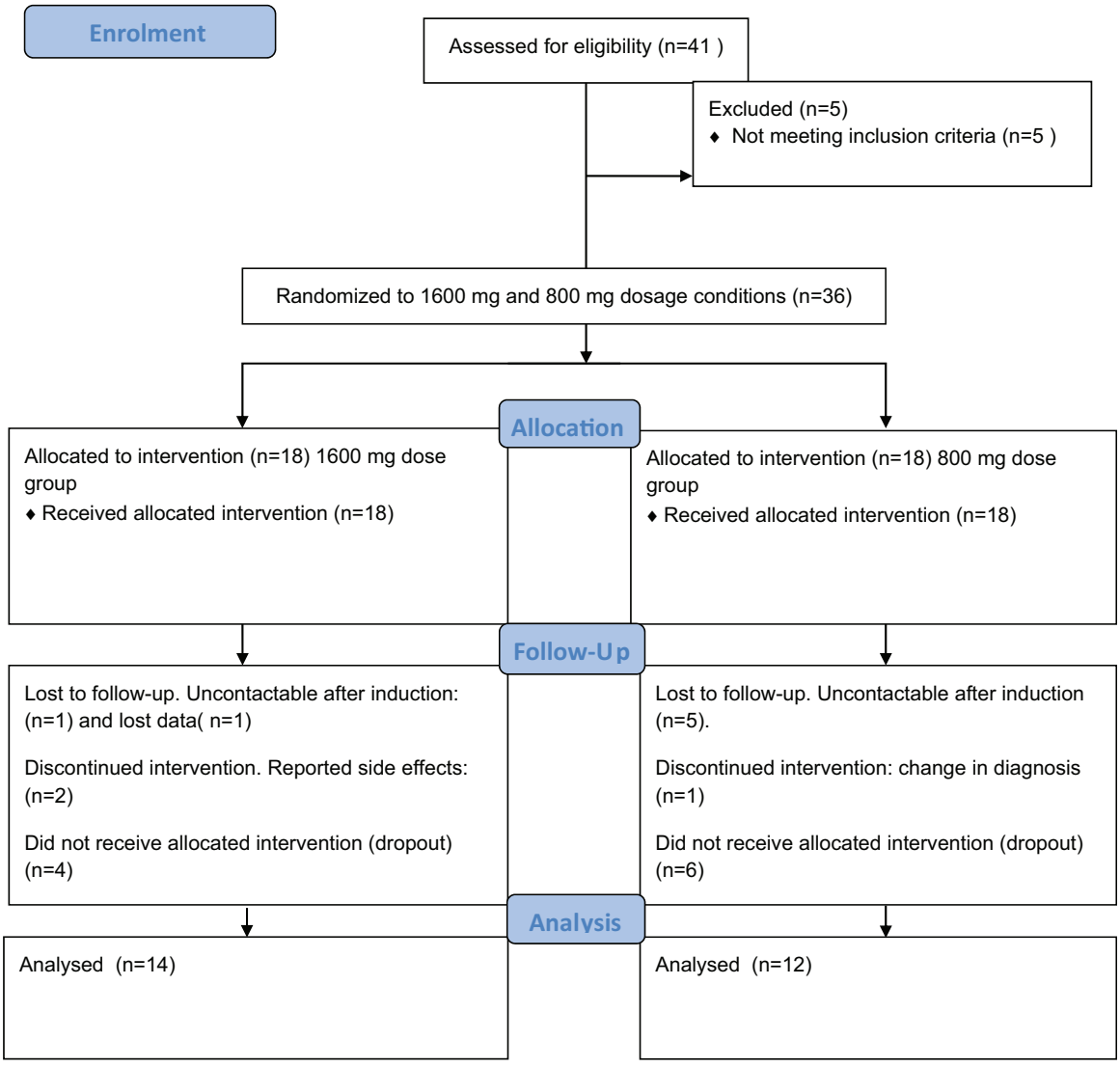

Fig. 1. Consort diagram.

depressive symptoms and symptom maintenance compared to administering low dose SAMe (800 mg per day).

2. The administration of a high daily dose of Magnesium Orotate (1600 mg per day) to participants who did not respond to SAMe would produce significant improvements in depressive symptoms based on alternative mechanisms to the traditional methylation processes typically applied.

2. Methods

This was a single centre, dosage condition blinded controlled study and was carried out according to the Declaration of Helsinki and written informed consent was obtained from all subjects. This study received ethical approval from the Medical Research Ethics Committee (MREC approval number 2012000647) University of Queensland, Australia, within the guidelines of the National Statement on Ethical Conduct in Human Research ANZCTRN12614000544673.

All participants were required to have a primary diagnosis of major depressive disorder (severe: ICD-DSM conversion) with a verifiable history of sub-optimal treatment response (at least three previous episodes) with current medication type being SSRIs (for standardisation purposes), and at least 18 years of age. Participants were also asked not to take any nutritional supplements that have antidepressant activity and a list was provided. Participants were excluded if they were taking nutritional supplements thought to have antidepressant effects, were a current high suicide risk, were not currently depressed, were experiencing psychosis, or had a diagnosis of bipolar disorder or were serious substance misusers as defined by ICD 10-DSM criteria. Given that there are personality and mood factors involved with the assessment and treatment of depression, a high degree of comorbidity on Axis I, II, III, the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV criterion), was accepted in this study. Complex mood, personality and health problems are typical in sub-optimal treatment response for depression [1,7].

Participants were recruited from June to October 2014 from the Department of Psychiatry at the Royal Brisbane Women's Hospital in Brisbane Australia where they were being treated for depression. Participants then attended an induction session consisting of baseline assessment including an International Classification of Diseases (ICD-DSM) diagnostic interview and the Structured and Clinical Interview for DSM-IV *Axis II* Personality Disorders (SCID-II) interview if indicated, and a series of self-reported measures for depression and anxiety and quality of life were administered.

Assessment was conducted by a practising clinical psychologist before participants were allocated to conditions for blinding purposes. Participants were blinded to the two different SAMe dosage conditions to which they were randomly allocated and the existence of the follow-up study assessing Magnesium Orotate.

After baseline assessment, 36 participants entered the study and were randomly assigned to the dosage condition. Participants were provided with a study pack consisting of a 15-week supply of SAMe and a daily dosage log that participants completed to ensure conformity to dosage protocol and to record issues such as side effects, missed doses and medication compliance and/or changes. Weekly symptom change was measured over the duration of the study as an alternate measure of treatment response. All participants were contacted fortnightly by phone to ensure conformity to the study protocol and encourage the timely return of data.

Study treatment included 1600 mg SAMe (the dose was 4 × 400 mg tablets 2 × b.i.d.) and 800 mg SAMe (the dose was 2 × 400 mg b.i.d.) and was donated by the Life Extension Foundation USA. The Magnesium Orotate was provided as 400 mg tablets (the dose was 4 × 400 mg 2 × b.i.d.).

2.1. Outcome measures for depression

This study used the Mini International Neuropsychiatric Interview (ICD-DSM MINI. 5) [26]; Beck Depression Inventory (BDI) [27]; Depression Anxiety Stress Scale (DASS) [28]; Structured Clinical Interview for DSM (SCID) [29]; Outcome Questionnaire 45 (OQ45) [30]; Warwick-Edinburgh Mental Well-being Scale (WBS) [31]; and Quality of Life Scale (QOL) [32]. The MINI and SCID were clinician administered whereas the BDI, DASS, WBS, OQ45 and QOL were self-report measures. The BDI, DASS and WBS assess mood through somewhat different factor structures and the DASS and WBS were used as confirmation of BDI self-assessment to ensure diagnostic validity due to small sample size and lack of controls. The confirmatory self-report assessment confirmed BDI results, suggesting a high degree of assessment validity. Only the primary outcome measures BDI, OQ45 and QOL will be reported below.

2.1.1. MINI

The Mini International Neuropsychiatric Interview (MINI 5) served as the primary clinician diagnostic tool administered at study baseline. Validation and reliability studies show that the MINI has acceptably high validation and reliability scores [26].

2.1.2. BDI

The BDI is a 21-item self-report inventory that is widely used to assess depression and was administered at study baseline and endpoint. It has high internal constancy and correlates highly with other self-report measures of depression (α = 0.60–0.90) [27].

2.1.3. SCID

Assessment for *axis II* was conducted using the Structured Clinical Interview for DSM (SCID) diagnostic interview and was administered at study baseline [29]. The SCID clinical interview has acceptable validity in diagnosing personality disorder $\kappa > .75$.

2.1.4. OQ45

The Outcome Questionnaire 45 (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 (α = 0.93 and $\kappa > 0.83$) and was administered at study baseline, and then weekly intervals for the study duration to plot symptom change [30]. The OQ45 consists of 45 items with a five point scale. A high total score >80 indicates a high level of symptom distress (anxiety, depression, somatic, work and social role problems). Lower scores indicate less severity of problems. Average community non-clinical scores cut off (CO) occur at <63 and changes of 14 points in either direction are considered clinically significant changes and deemed research reliable. As the OQ45 measures reliable change over time it can detect short-term symptom and unstainable change that may be indicative of placebo effects [30].

2.1.5. QOL

Quality of Life Scale (QOL) modified has 16 items and evaluates perceived satisfaction with life over a number of domains (α = 0.85) and was administered at study baseline and endpoint [32]. Quality of life typically provides an important evaluation of perception of life circumstances and stressors.

2.2. Statistical analysis

T–tests were performed on continuous normally distributed variables, and Chi-square tests on categorical variables. These were performed to investigate the difference in pre- and post-supplementation scores for total group treatment effect. Repeated measures analysis of variance (ANOVA) was conducted to investigate the interaction between the treatment groups. The significance level was set at $p < 0.05$. All data was presented in tabular and graphic forms. Data were visually inspected for normality on scatter plots and fell within normal distributions for means vs. median scores. Homoscedasticity for both groups was confirmed by Levene's test (p = 0.86).

3. Results

All participants had a primary diagnosis of MDD with 98% of participants having a variety of comorbid diagnoses. Participant age ranged between 28 and 70 years [49.4 ± 10.6 years (mean ± SD)] which was not significantly different between conditions [$F(4.\ 34) = .502$; $p = .15$] (see Table 1). Twenty-two participants were female and (n = 14) males. Participants were evaluated for comorbid psychiatric disorders, health problems and previous trauma. There was no significant difference in distribution of comorbid psychiatric disorders [$\chi^2(2) = 1.86$; $p < .089$]; health problems [$\chi^2(2) = 1.86$; $p < .089$] or previous trauma [$\chi^2(2) = 3.99$; $p < .062$] between dosage groups. Participant dose logbooks indicated high supplement compliance, with no reported missed doses. However, there was some minor variation on dosage times noted for most participants that did not exceed 60 min for morning or evening doses.

There was a moderate rate of participant drop out, six participants were not able to be contacted with repeated follow up phone calls after induction, one participant reported losing their data, two withdrew due to GIT side effects reported as indigestion and mild intestinal cramps (1600 mg group) and one due to an additional psychiatric diagnosis (800 mg group) making them unsuitable for continued participation. This resulted in an incomplete data set of (n = 10) cases with no late term or endpoint data. Non-completer data was included as a preliminary intention to treat analysis and did not significantly affect interval or outcome scores and was removed for the full data analysis of (n = 26). In the 800 mg condition (n = 12) six participants were female and in the 1600 gm condition (n = 14) seven participants were female.

To assess the effect of SAMe a preliminary combined group analysis was conducted. Total SAMe group pre- and post-change scores were subjected to a two-way analysis of variance. The main effect of BDI change was a statistically significant reduction of symptom scores [$t(18) = 16.48$; $p \leq 0.001$] from (mean ± SD) 38.2 ± 7.9 to 11.4 ± 8.5 for endpoint. Fifty-two percent of the total group was in clinical remission by study endpoint and 24% remained

mildly depressed. A placebo change statistic was added as a covariate [19]. After taking the placebo adjusted effect on BDI change into account, the main effect of BDI change was statistically significant [$t(18) = 14.0$; $p = 0.01$] indicating a 35% remission rate (Table 2).

The main effect of OQ45 change was a significant reduction in functional distress scores [$t(18) = 7.80$; $p \leq 0.001$] from (mean ± SD) 113.9 ± 15.1 to 57.0 ± 24.0. The ratio of variance accounted for by change across all measurement points was strong [partial eta^2 = 0.91]. The main effect of QOL change was significantly increased quality of life scores [$t(18) = 8.21$; $p \leq 0.001$] changing from (mean ± SD) 53.8 ± 12.5 to 75.0 ± 19.1 (Fig. 2).

In regards to our hypothesis, the 2 group analysis revealed no significant differences between the 1600 mg and 800 mg groups on BDI [$F(1.\ 26) = .256$; $p = .618$]; QOL [$F(1.\ 33) = 0.000$; $p = .983$]; and OQ45 [$F(1.\ 914) = 0.015$; $p = 0.982$].

Treatment symptom response reached the clinical cut off by week 6 [>63 OQ45] in the 1600 mg group and by week 8 in the 800 mg group. However, this difference was not significant [$F(1.19) = .002$; $p = 0.961$]. At week 6 the change from baseline was (mean ± SD) 54.5 ± 25.8 to 55.5 ± 21.3 by week 8. OQ45 interval symptom scores over the 15 week duration of the study were not significantly different between the 1600 mg and 800 mg group condition revealing no difference in symptom maintenance and relapse between conditions [$F(1.10) = 0.124$; $p = 0.429$].

4. Magnesium Orotate administration

At the completion of the 15 week study duration, ($n = 8$) suboptimal treatment responders ($n = 5$ from the 1600 mg group and $n = 3$ from the 800 mg group) were inducted into the Magnesium Orotate phase of the study after a 2 week SAMe wash out period. Sub-optimal treatment responders were defined as those still experiencing MDD by the SAMe study endpoint which consisted of ($n = 6$) MDD severe (ICD-DSM), ($n = 2$) MDD moderate and ($n = 6$) were female aged between 33 and 70 years [mean ± SD, 50.9 ± 10.5 years]. The Orotate phase of the study followed the same protocol as for the SAMe phase. However as a simple investigation of efficacy of Orotate only, this phase was conducted as a single group for 8 weeks duration. Participants were blinded to the medication type (provided in plain plastic bottles) and dose. Participants provided feedback attesting to the tolerability of Magnesium Orotate and rapid subjective sense of improvement especially regarding energy levels (Table 3).

Table 2
SAMe pre- and post-treatment data study completers.

Baseline scores	Group 1: 1600 mg SAMe $n = 14$ (mean ± SD)	Group 2: 800 mg SAMe $n = 12$ (mean ± SD)
BDI	35.5 ± 6.9	40.8 ± 9.3
OQ45	110.1 ± 13.4	119.0 ± 18.0
QOL	55.0 ± 11.5	52.5 ± 15.0
Endpoint scores	Week 15	Week 15
BDI	10.0 ± 9.3	8.0 ± 8.7
OQ45	58.5 ± 25.5	55.0 ± 27.7
QOL	83.0 ± 16.9	76.0 ± 24.5

BDI, Beck Depression Inventory; OQ45, Outcome Questionnaire 45; QOL, Quality of Life Scale.

The BDI score for the total Orotate group $n = 8$ at baseline (after 2 weeks wash out from SAMe study) was 33.8 ± 7.1. The main effect of BDI change was significant with a reduction in symptom scores [$t(7) = 12.4$; $p = 0.001$] to 14.1 ± 12. Fifty percent ($n = 4$) of the total group was in remission by study endpoint, 30% ($n = 2$) remained moderately depressed, 10% ($n = 1$) had mild depression and 10% ($n = 1$) did not experience any clinical change and remained with MDD severe (Table 4).

The main effect of OQ45 change was significant [$t(7) = 10.7$; $p \leq 0.001$] indicating reduced functional distress scores from a mean of 86.6 ± 25 to 54.2 ± 9.4. The ratio of variance accounted for by change across all measurement points was moderate (partial eta^2 = 0.75) (Fig. 3).

The main effect of QOL change was significant with increased quality of life scores [$t(7) = 10.7$; $p = 0.001$] from 55.2 ± 8.6 to 76.0 ± 24.5.

5. Discussion

Both SAMe dosage groups experienced significantly reduced symptom scores on BDI and OQ45 by 6 weeks which is a similar response time reported in previous adjunctive research [19]. For treatment responders, their clinical gains were well maintained across the 15 weeks and equated with reduced symptoms, distress and improved functioning with no relapse as measured by the OQ45. There was good compliance with the supplement protocol and prescribed SSRI medication. There was no reported additional psychopharmacological intervention in the sample throughout the study duration.

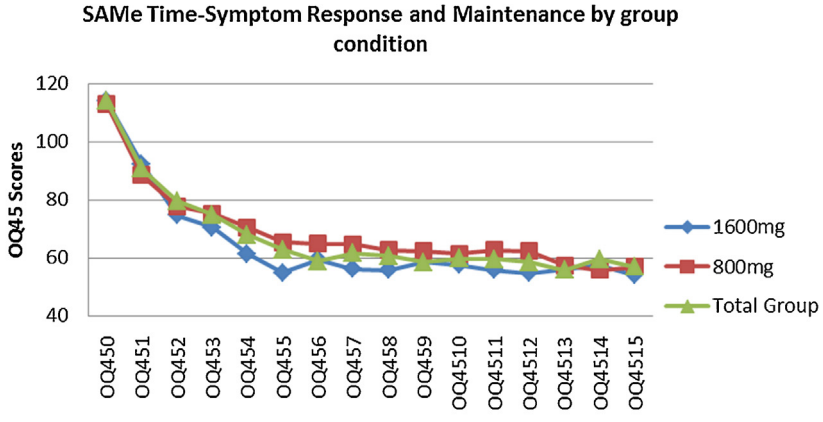

Fig. 2. SAMe weekly interval symptom response scores OQ45. Axis A = OQ45 scores range reported from baseline to study completion. Axis B = OQ45 scores from intake week = 0 to endpoint week = 15.

Table 3
SAMe non-responders at week 15 who were subsequently recruited into the Magnesium Orotate condition.

Assessments	Week 15 BDI ($n=8$) (mean ± SD)	
BDI	31.0 ± 8.5	*N*
MDD + AD		5
MDD+ PTSD		1
MDD+ PD		2
Health comorbidity		8

Table 4
Baseline and week 8 scores for Orotate (1600 mg) group recruited from the SAMe non-responders.

Assessments	Baseline $n=8$ (mean ± SD)	Week 8 $n=8$ (mean ± SD)
BDI	33.8 ± 7.1	14.1 ± 12
OQ45	86.6 ± 25	54.2 ± 9.4
QOL	55.2 ± 8.6	76.0 ± 24.5

Our hypothesis was not supported for prescribing a higher dose over a lower dose of SAMe (1600 mg versus 800 mg) and both doses appeared equally effective for symptom maintenance. Doses as low as 400 mg per day intramuscularly have been reported in non-augmentation SAMe studies with acceptable results. Translating injectable delivery doses to orally delivered SAMe is difficult, however SAMe is known to be highly bioavailable [10]. We consider it likely that 800 mg a day of SAMe is the required therapeutic dose for treatment response with a higher dose not providing additional benefit. Both dosage forms resulted in significant and meaningful improvements in mood and quality of life for the majority of participants. Importantly the placebo adjusted response rate as measured by BDI was consistent with findings from a previous adjunctive study [19]. While it is problematic using a statistical method from a different study, it provides a method of controlling for potential placebo effects in the analysis.

As reliable significant clinical change was confirmed by the OQ45 across treatment responders without relapse, and given the long duration of the study this would suggest a low likelihood of a significant placebo effect being operative in the treatment responsive group. It is also of interest that the sample had multiple health problems and comorbid diagnoses which did not significantly impact on treatment response. The importance of comorbid disorders on treatment response in depression is generally thought problematic but not always an impediment to treatment. However, replication with a larger sample is required to explore patient characteristics that may enhance or impede treatment response. The only reported side effects were GIT cramps and indigestion by two participants in the 1600 mg SAMe group. While not a common side effect, GIT cramping has been reported by a small proportion of SAMe users in previous studies at higher doses [17,18].

From the (n = 8) Magnesium Orotate plus SSRI participants who did not respond to the SAMe plus SSRI trial, (n = 7) achieved a significant clinical response to the Magnesium Orotate, and (n = 1) experienced no change. There was significant reduction in BDI scores with half the cohort in remission and all but one of the remaining participants significantly improved by study endpoint. Mean OQ45 scores indicated remission by week 6, which was a similar response time as the SAMe treatment. Likewise, the QOL scores suggested greater satisfaction and engagement with life for responders.

These results while preliminary, suggest the importance of further investigation of Orotate as this group were non-responsive to the SAMe adjunctive protocol. The small numbers in this study warrant a high degree of caution in drawing conclusion although it might be concluded that that SAMe and Magnesium Orotate could be important targets for further research.

We propose that the potential efficacy of these compounds may be in part related to their interaction with the GIT microbiome. We have previously made the case that treatment response implicates the GIT microbiome [25]. There is evidence to suggest that poor treatment response in depression is associated by an unbalanced GIT microbiome in favour of a low level sustained pro-inflammatory profile with by-products that affect peripheral and CNS communication with negative consequences for hippocampal protein synthesis and brain neurotransmitter synthesis. This scenario may also down regulate the production of metabolites normally created during absorption of therapeutic agents. It is plausible that these metabolites may be biologically active and important for treatment response [25]. However, whether this GIT microbiome dysfunction (dysbiosis) is associated with sub-optimal treatment response is not yet established [25,33]. Orotic acid is produced by the intestinal bacteria and plays a role in the synthesis of DNA and RNA and influences systemic functions and has a known anti-inflammatory effect [24]. Likewise, SAMe and its

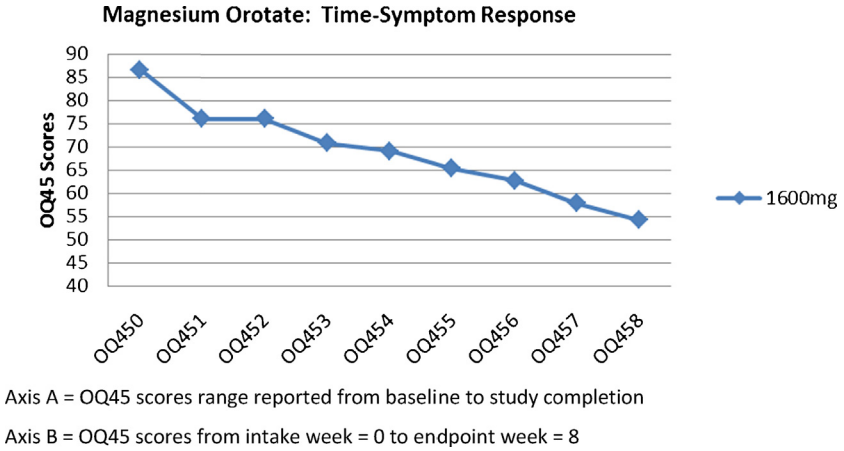

Fig. 3. Magnesium Orotate weekly interval symptom response scores OQ45. Axis A = OQ45 scores range reported from baseline to study completion. Axis B = OQ45 scores from intake week = 0 to endpoint week = 8.

metabolites may modulate receptors within the GIT. SAMe has anti-inflammatory activity which directly impacts some classes of pro-inflammatory bacteria and favourably modulates hypothalamic-pituitary-adrenal (HPA) functioning via the GIT independent of effects once absorbed. As an impaired microbiome may be involved in sub-optimal response to oral treatments due to inflammation, impaired absorption, metabolite production, and receptor signalling [33,34], the use probiotics to correct GIT dysfunction and improve treatment response requires further investigation [25].

6. Limitations

There are several limitations with this study that caution the interpretation of the results. As a pilot study, the sample was not sufficient to generalise results to the sub-optimal treatment responder population. Likewise, the study design while robust in terms of assessment and treatment response measurement was limited by the lack of a placebo arm. However, as a pilot study of SAMe and Orotate we consider that the results indicate the need for further investigation of these adjunctives due to the lack of tolerable pharmacologic treatment options for this group of patients. Future investigations should include an examination of GIT dysfunction and repair with specific probiotic strains, in robust placebo controlled studies.

Author contributions

MB, LV conception and design of study. MB, LV, SC read, amended and approved the final version of the manuscript.

Conflicts of interest

The authors have no further conflicts of interest relevant to the content of this study.

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