(S)–S-adenosylmethionine in the treatment of pre-menstrual disorders in adult women: A protocol for an open-label pilot study

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ABSTRACT

Pre-menstrual disorders, including pre-menstrual syndrome and pre-menstrual dysphoric disorder, are highly prevalent disorders in women of reproductive age. Pre-menstrual disorders are associated with debilitating symptoms that onset in the days prior to menses. A complex interplay between hormonal fluctuations, cellular sensitivity, and psychosocial stressors likely underly the pathophysiology of pre-menstrual disorders. Current treatment options include selective serotonin reuptake inhibitors, hormonal therapies, and psychosocial support. There is growing evidence for oestrogen, progesterone, gonadotropin Releasing Hormone analogues and Complementary and Alternative Medicines in treating Pre-menstrual disorders. (S)–S-adenosylmethionine is a complementary and alternative medicine with postulated roles in the treatment of depression, with a rather rapid onset of action and minimal side effect profile. We propose a protocol for investigating the efficacy of (S)–S-adenosylmethionine in the treatment of pre-menstrual disorders. The proposed study is an open label pilot study, that will recruit thirty women between the ages of 18–45 who experience a pre-menstrual disorder. Daily and interval questionnaires will provide a quantification of symptoms across four menstrual cycles (16 weeks). During two consecutive menstrual cycles it is proposed that participants receive oral (S)–S-adenosylmethionine Complex 400 mg three times a day (total daily dose 1200 mg), during the pre-menstrual time-period (14 days prior to menses). Changes in pre-menstrual disorder symptoms between control and treatment cycles will assist in elucidating the clinical efficacy of (S)–S-adenosylmethionine. This study has the potential to support a larger double blinded, placebo controlled randomised control trial and aims to enrich the knowledge surrounding pre-menstrual disorders.

1. Background

The menstrual cycle is often accompanied by physical and psychological distress, with up to 80% of women experiencing mild symptoms such as bloating, breast tenderness, irritability and pain leading up to menstruation [1]. It is estimated that 13–47% of women of reproductive age experience a constellation of symptoms termed Pre-Menstrual Syndrome (PMS) [2]. At the severe end of the spectrum is Pre-Menstrual Dysphoric Disorder (PMDD), associated with debilitating symptoms that impair an individual's daily functioning [3]. The prevalence of confirmed PMDD diagnosis is estimated at 1.6–3.7%, with a higher number of women having a provisional diagnosis [3]. These disorders will collectively be termed Pre-Menstrual Disorders (PMDs). The debilitating symptoms of PMDs, particularly PMDD, onset during the luteal phase and are comparable to those of major depression disorder [4]. The

economic impacts of PMDD are largely related to loss of productivity [5].

1.1. The cause

The pathogenesis of PMDs appears to involve a complex interplay between endocrinological signalling, neurochemical susceptibility and psychosocial stressors [6–9]. From a biochemical perspective, the literature exploring the roles of oestrogen, progesterone and their associated fluctuations during the menstrual cycle have been discussed extensively elsewhere [10]. Pertinent to PMD pathophysiology appears to be a decline in the neuroprotective hormone oestrogen levels during the luteal phase, accompanied by a dynamic rise and rapid fall of progesterone in the late luteal phase, with fluctuations in the associated progestogenic metabolite alloprogesterone (ALLO) [11–14]. ALLO is an

allosteric agonist of the neuroinhibitory GABA-A receptor, with animal PMD models replicating PMD-like symptoms through progesterone and ALLO withdrawal [15–17]. The knowledge surrounding the role of progestogens in PMD is ever evolving, including researching exploring the role of novel ALLO modulators in the treatment of PMDs [18].

From a psychosocial perspective stress, substance use, negative self-perceptions, high trait neuroticism and negative cognitive styles are higher in those individual's with PMDs, and are often related to increased symptom severity [7,19]. PMDs have a high prevalence in those individuals with low education levels and those who are unemployed [20]. Traumatic early life experiences, including sexual abuse and emotional neglect, appear to predispose an individual to PMDs, and often increase symptom severity through emotional regulation difficulties [21]. A diagnosis of Post-Traumatic Stress Disorder (PTSD) also appears to predispose an individual to a later diagnosis of a PMD [22]. The psychosocial components of PMDs call for a holistic approach to treatment.

1.2. Current treatments

The treatment approach to PMD often involves a combination of psychotropic medications and/or hormonal therapy, adjuvant psychotherapy and lifestyle optimisation [23]. The individual's care is ideally coordinated by a general practitioner with input from a gynaecologist and mental health service. Serotonergic agents, such as Selective Serotonin Reuptake Inhibitors (SSRIs) are the first-line pharmacological agents for the treatment of PMDs [14]. A range of SSRIs (sertraline, fluoxetine, paroxetine, and escitalopram) and some Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs) (venlafaxine), have demonstrated efficacy in treating psychological, somatic, and behavioural symptoms of PMDs [14,24]. It has been suggested that many SSRIs may improve PMDs symptoms through the modulation of ALLO levels [25,26]. The effects of SSRIs on ALLO in PMDs may explain the rapid symptom improvement following administration, compared to the delayed effects in depression [27,28]. As such, there is evidence to support intermittent 14-day luteal dosing of some SSRIs including fluoxetine, paroxetine, and sertraline in PMDs [29]. Head-to-head trials are required to compare the efficacy of continuous compared to intermittent dosing [24]. Importantly, there does not appear to be increased withdrawal effect in intermittent compared to continuous dosing [14]. Despite these promising findings, many individuals report common side effects of SSRIs, which may preclude their use and result in discontinuation despite clinical efficacy [14,30].

Hormonal therapies include the Combined Oral Contraceptive Pill (COCP), which contain oestrogen and progesterone are involved in key neurochemical pathways. Oestrogen is often termed neuroprotective and has been shown to reduce depressive symptoms, whilst high progesterone containing COCPs appear to worsen mood symptoms [31]. Evidence supports COCP use in reducing overall PMDs symptomology, with limited evidence for treating premenstrual depressive symptoms [29,32]. Currently, there is evidence to suggest efficacy of ethinyl estradiol 20μg/drospirenone 3 mg COCP in a 24-day active, 4-day placebo regime compared to placebo [33]. COCPs containing specific formulations of orally active progesterone, such as nomegestrol acetate compared to drospirenone, have been postulated to be more efficacious due to fewer androgenic effects [34]. However, recent evidence suggests equivalent efficacy of COCP formulations [32]. Continuous dosing of COCP has been proposed to reduce hormonal fluctuations associated with PMD symptoms, suppress ovulation, and reduce PMD symptoms [34]. Head-to-head trials comparing intermittent to continuous dosing are warranted. An alternative hormonal approach to reducing endocrinological fluctuations includes the use of Gonadotropin Hormone-Releasing Hormone (GnRH) analogues which act via negative feedback at the hypothalamic pituitary axis [14,35]. These approaches are reserved for severe, unremitting cases of PMDD and often induce menopause-like symptoms requiring hormonal add-back therapy that

can result in PMDD symptom recurrence [14,35,36]. Progesterone antagonists, such as ulipristal acetate (UPA), when used at low doses also induce anovulatory menstrual cycles in up to 80% of women. Emerging evidence suggests that UPA treatment may improve the symptoms of PMDD through ovulatory suppression, with reduced hormonal fluctuations, and through other actions mediated by progesterone receptor antagonism [37]. The numerous contraindications to hormonal therapy, alongside individual preferences for non-hormonal treatment presents as barriers to their use.

1.3. Alternative treatments

Complementary and Alternative Medicines (CAMs) are an area of research interest, which may appeal to individuals with a desire for alternative approaches or who have contraindications to first-line therapies [36]. Clinical guidelines often acknowledge the conflictual evidence for the efficacy of CAMs in PMDs and as such they are not currently a first line treatment [14,23]. A CAM not yet explored in PMDs is (S)–S-adenosylmethionine (SAMe), a physiological co-substrate involved in various intracellular metabolic pathways [32]. SAMe is a pleiotropic cellular mediator, with proposed roles in the treatment of depression, liver disease, osteoarthritis and Alzheimer's disease [38]. In Australia and The United States, SAMe is available as an oral CAM, whilst it remains prescription only in many countries [38,39]. SAMe is also active in intravenous and intramuscular formulations [40,41].

1.4. SAMe background

SAMe was discovered in 1952 and its use in the treatment of depression arose from clinical trials in the 1970's [42,43]. A Cochrane review explored evidence surrounding the use of SAMe in depression treatment as either monotherapy compared to placebo, monotherapy compared to Tricyclic Antidepressants (TCA) such as imipramine or the SSRI escitalopram, or as an add on for the treatment of depression [44]. Researchers concluded that SAMe was no more efficacious than placebo as monotherapy, was comparable to that of imipramine and escitalopram, and that there was no significant difference in drop-out compared to other antidepressants studies. There was limited evidence to suggest SAMe was more efficacious as an adjuvant add-on therapy to augment SSRI treatment compared to placebo. The evidence been listed as low to very low in quality with significant heterogeneity, warranting further high-quality studies [44]. A more recent systematic review found a decrease in depressive symptoms in three out of five studies comparing SAMe and placebo, but no superior efficacy when compared to escitalopram or imipramine [45]. In these studies, the dose ranged from oral SAMe at 200–3200 mg/day and intramuscular at 200 mg/day and was overall well tolerated, with transient 'mild' side effects [45]. Preliminary data suggests that SAMe can decrease depressive symptoms within one week at doses of up to 800 mg twice a day, as demonstrated in a sample of individuals with co-morbid HIV/AIDS [46]. The rather rapid onset of mood improvement is favourable in the treatment of a cyclical mood disorders, such as PMDs, where intermittent relief is required. SAMe Mechanism.

The mechanisms through which SAMe exerts its potential antidepressant effects remain unclear. Endogenous SAMe appears to be uniformly distributed across the brain [47]. Rodent models have demonstrated an increase in 5-HT and 5-HIAA (a key serotonergic metabolite) in both the forebrain and brainstem following SAMe administration, and alterations subcortical noradrenaline levels [48,49]. SAMe has been shown to increase autonomic receptor density in rodent studies investigating the effects of SAMe on ageing, including that of muscarinic (M1) and β-1 adrenoreceptors in the striatum, pineal gland, and cortex [50,51]. The ability of SAMe to modulate the metabolism of biological amines and receptor expression is possibly related to its role in methylation of neurotransmitters, phospholipid membranes and intracellular proteins [38,52]. Further studies are warranted to elucidate

the intracellular and neurochemical effects of SAMe administration.

1.5. SAMe tolerability

The literature suggests that SAMe is largely well tolerated, with common side-effects including gastrointestinal discomfort (nausea, vomiting and diarrhoea), with some reports of excessive sweating, dizziness, anxiety, tachycardia and restlessness [45]. These symptoms appear to be dose dependent, with doses up to 1800 mg daily being well tolerated [53,54]. Notable serious side-effects include mood elevation and the precipitation of hypomanic symptoms and manic episodes in those with a history of bipolar affective disorder [55,56]. Hypomanic symptoms and a transient mixed manic episode have also been observed in two different study participants, with a third study participant developing a manic episode who had no documented history of bipolar affective disorder (BPAD) [54,57,58]. SAMe should therefore be avoided in patients with a personal or family history of BPAD. In terms of other contraindications and precautions, there is limited evidence surrounding the use of SAMe during pregnancy and breastfeeding. One study investigated the effects of 20-days of 900 mg intravenous SAMe in pregnant women with cholestasis [59]. No adverse effects were reported in infants whose mothers were treated with SAMe during gestation at a three-month follow-up. However, due to the lack of rigorous evidence, the possibility of teratogenicity cannot be excluded.

SAMe has few reported drug interactions, with a single case report of serotonin syndrome when SAMe was administered in conjunction with escalating doses of clomipramine, a TCA [60]. Despite this, SAMe is reported to have been safely used to augment antidepressants, including monoamine oxidase inhibitors and SSRIs [41,47,61–63].

SAMe appears to be a safe alternative therapeutic with a limited side-effect profile in individuals who do not have a history of BPAD and are not pregnant. When considering the treatment elusive nature of PMDs, cyclical onset of symptoms, and the rather fast onset of the action of SAMe, further research is warranted. To the authors knowledge studies evaluating the use of SAMe in PMDs have yet to be conducted (see Table 1).

2. Methods

Here we propose a protocol for an open-label pilot study to determine if oral SAMe treatment, as SAMe 400 Complex, reduces the psychological and somatic symptoms of PMDs. This study proposes to recruit 30 menstruating individuals between the ages of 18–45 years old who have received a prior diagnosis of a pre-menstrual spectrum disorder, including PMS or PMDD, or meet the criteria for diagnosis as per the Diagnostic and Statistical Manual Version Five (DSM-V) at recruitment [4]. Inclusion and exclusion criteria can be found in Table 1. The proposed methodology has been summarised in Fig. 1 and Table 4 and will be detailed below, whilst further details on survey tools are summarise in Tables 2 and 3.

2.1. Baseline interview

Participants will be instructed to complete two questionnaires, the Depression and Anxiety Symptom Scale-21 (DASS-21) and Side-effect and Adverse Events (SAE) scale following screening and consent. Demographic data will be collected including level of education, occupation, and ethnicity, alongside medical, surgical, gynaecological, psychiatric history including previous treatments (pharmacological and non-pharmacological), family history and allergies.

2.2. Intervention

As an open label trail all eligible and consenting participants of the study will receive treatment during the study. SAMe dosing regimens range from 400 to 3200 mg per day, with side-effects increasing at doses

Table 1
Inclusion and exclusion criteria for participation.

Inclusion	Exclusion
●Women aged between 18 and 45. ●Prior diagnosis of a Pre-Menstrual Disorder (PMS or PMDD) or meeting criteria for diagnosis as screened during recruitment. ●Proficient in both reading and writing in English.	●Pregnant or lactating women. ●Women less than one-year post-partum. ●Taking hormone replacement therapy and hormonally based contraceptives, including the Combined Oral Contraceptive Pill (COCP), etonogestrel implant (Implanon), intrauterine levonogestral devices (Mirena), transdermal oestradiol patches or depot progesterone injections. ●Concurrent treatment with psychotherapy including counselling, structured psychotherapy, and psychodynamic psychotherapy. ●Concurrent treatment with psychotropic medications including use in the past four weeks (to allow for drug wash-out [64] such as serotonergic agents, monoamine oxidase inhibitors or other forms of antidepressants, including atypical antidepressants such as agomelatine. ●Comorbid renal, hepatic impairment, haematological, oncological, or cardiovascular disease. ●Alcohol use disorder ●Substance use disorder requiring intervention or rehabilitation in the last three months ●Woman taking other complimentary alternative medicines, including cannabinoid containing agents such as cannabidiol (CBD) products.

of 3200 mg [45,68]. Oral SAMe reaches peak plasma concentration three to 5 h following oral administration and has an approximate half-life of 100 min, therefore a split dosing regimen is favoured [68]. For these reasons SAMe 400 Complex treatment will be administered, as SAMe 400 Complex 1200 mg oral per day (as 400 mg SAMe 400 Complex three times per day) during the luteal phase of the mental cycle (for 14-days prior to menstruation) for two consecutive menstrual cycles.

Dosing schedule of SAMe 400 Complex is as follows (Fig. 1).

- 1st week up to week 11: No active treatment
- 11th week up to week 13: SAMe 400 Complex 1200 mg/day (as one 400 mg tablets three times a day) for 14 days prior to menses
- 13th week up to week 15: No active treatment
- 15th week up to week 17: SAMe 400 Complex 1200 mg/day (as one 400 mg tablets three times a day) for 14 days prior to menses

SAMe 400 Complex will be provided to participants by mail as a total of 82 tablets per participant, to be self-administered as one tablet three times a day for a total of 28 days (across 14-day pre-menstrual periods in two menstrual cycles).

Control menstrual cycles: Participants will be asked to complete a daily questionnaire of menstrual symptoms starting from the first day of their menstrual cycle at the commencement of the study, and daily for the duration of the study. Participants will be asked to complete a urine ovulation test 21 days after the onset of their previous menstrual period until they return a positive result. This will assist in correlating ovulation with symptom onset in the menstrual cycle. Participants will then complete a questionnaire pertaining to depression, anxiety, and stress symptoms on day one of their next menstrual cycle. This will be an untreated or control menstrual cycle (approximately 28 days), titled 'Cycle One, First Control Cycle'. Participants will then complete a second untreated control menstrual cycle, titled 'Cycle Two, Second Control

Table 2
Study measurements.

PMDD Daily Symptom Measurement	The Daily Record of Severity of Problems (DRSP) Questionnaire is a 21-item questionnaire assessing mood and physical symptoms, alongside the social impacts of symptoms. The DRSP will be completed starting on the first day of menstruation in as previously deemed acceptable [65]. This questionnaire has been previously validated with high internal and external validity [66].
Mood Symptom Measurement	The 21 Item Depression, Anxiety and Stress Scale (DASS-21) is a shortened version of the original 42-item scale and will be used as a measure of the psychological symptoms of PMDD. Research staff will be notified if a participant scores 'Extremely Severe' across any of the DASS-21 domains (depression score 28+, anxiety score 20+, stress score 34+). This will prompt the primary investigator to contact the participant via telephone to explore these symptoms further. The DASS-21 is used extensively both in the clinical and research setting and has high internal and external validity [67].
Safety and Tolerability Measurements	Pregnancy tests will be provided to participants via postal service. Each participant will be required to complete a pregnancy test prior to SAMe 400 Complex treatment cycles. The pregnancy test result is to be recorded on the online portal. A negative pregnancy test result is required before commencing each SAMe 400 Complex cycle. Participants are instructed to advise investigators if they return a positive pregnancy test. The Structured Adverse Effects (SAE) questionnaire will be administered. The research staff will be notified of completed SAE responses and assess the responses. Research staff will be notified of any responses listed as 'severe' by the participant which will prompt the primary investigator to contact the participant via telephone.
Clinical Measurements	Ovulation tests will be completed by participants to demark the mid-luteal phase. Once a positive ovulation test is recorded, participants will record this response on the REDCap platform. This response will be used to correlated symptoms recorded on the DRSP and DASS-21 with ovulation timing, as indicated by the presence of a Luteinising Hormone (LH) surge during ovulation.

Cycle'. At this point participants will have completed two control (untreated) menstrual cycles (Fig. 1, Table 4). Treatment menstrual cycles: Participants will then complete two treatment cycles, titled 'Cycle Three, First Treatment Cycle' and 'Cycle Four, Second Treatment Cycle'. That is, they will continue to record symptoms for 13 days, and then complete a urine pregnancy test prior to commencing oral 1200 mg daily SAMe 400 complex (as 400 mg oral SAMe three times daily) for the next 14 days. Participants will repeat the urine ovulation test 21 days after their last menstrual period until they return a positive result. On day one of their menstrual cycle, participants will repeat the depression, anxiety and stress symptom questionnaire and complete a questionnaire about any adverse effects they are experiencing. This treatment cycle will repeat once with another urine pregnancy test, 14-days of SAMe 400 Complex (as 400 mg oral SAMe three times daily) for the next 14 days prior to menstruation, a urine ovulation test and repeat questionnaires (Fig. 1, Table 4). The end of 'Cycle Four: Second Treatment Cycle' will be followed by a study conclusion interview and result feedback session with the investigators which will demarcate the end of the study protocol for that participant.

Table 3
Summary of study evaluations including the domain assessed, number (#) of items, estimated time to complete, and whether the measurement is a self-report and validated.

Domain	Tool	# Items	Duration	Self-report?	Validated?
Global Assessment of Pre-Menstrual Symptoms	The Daily Record of Severity of Problems (DRSP)	14	~5 min	Yes	Yes
Mood Symptoms (Depression, Anxiety, Stress)	The 21-item Depression and Anxiety Scale (DASS-21)	21	~5 min	Yes	Yes
Adverse Events	Structured Adverse Effects (SAE)	10	5 min	Yes	No
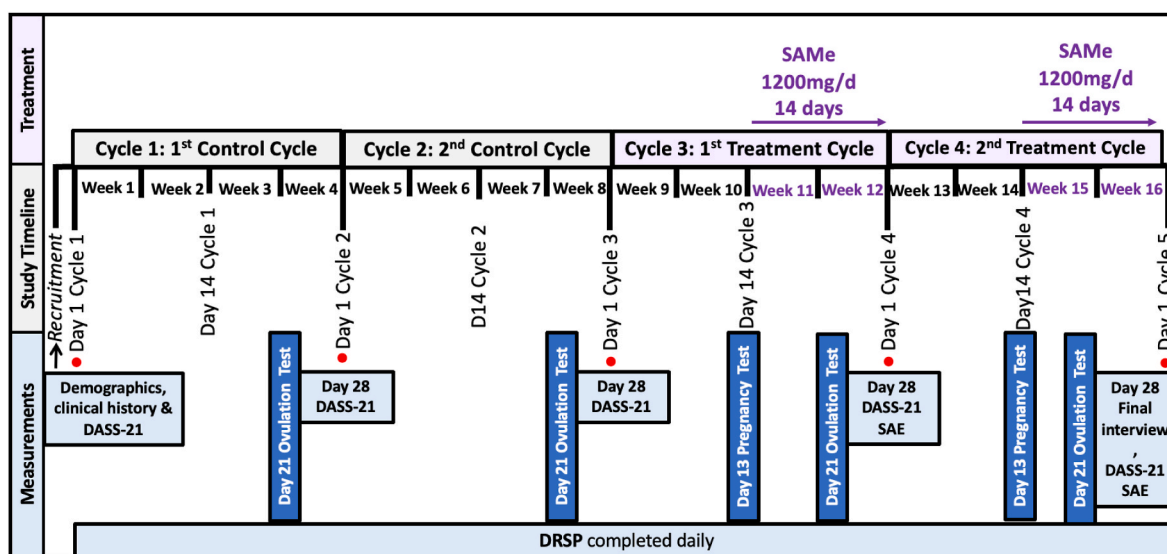
Fig. 1. A schematic outline of the proposed study treatment phases (SAMe 1200 mg per day over 14-day intervals) and measurements, including the Daily Record of Severity of Problems (DRSP), Structured Adverse Events (SAE), the Depression Anxiety Stress Scale-21 Item (DASS-21), physiological measurements (urine pregnancy and ovulation tests) and clinical interviews (demographics, clinical history, and final interview) in relation to the study timeline. Where ● indicates the first day of each menstrual cycle (first day of menstrual bleeding).

Table 4

The frequency of assessments to be completed online for each allocated timepoint of the study.

Cycle		C1: First Control Cycle				C2: Second Control Cycle				C3: First Treatment Cycle				C4: Second Treatment Cycle				
Timepoint	SCR	W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12	W13	W14	W15	W16	End
Teleconference Interview	x																	x
Informed Consent	x																	
Safety and Diagnostic Measures																		
Demographics	x																	
Medical/psychiatric History	x																	
Structured Adverse Events Questionnaire	x												x				x	
Research Measures																		
DRSP (daily)		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Pregnancy test (day 14)												x				x		
Ovulation test (day 21)				x				x				x				x		
DASS-21 (day 28)	x				x				x				x				x	
Intervention																		
SAM-E dosing												1200 mg /day	1200 mg /day			1200 mg/day	1200 mg /day	

2.3. Sample size

For this pilot study, a sample size of 30 participants will be utilised in the primary assessment of the feasibility of the study protocol and to assess preliminary effects of SAMe 400 Complex in PMDs. The sample size has been selected according to the literature which suggests that 30 participants are generally large enough to determine the feasibility of procedures and methods [69]. Over a three-month period, it is predicted that 30 participants can be recruited to participate in this study. A within-subjects design is proposed, with participants completing control cycles prior to treatment cycles. This is justified in determining the protocol feasibility and gathering preliminary data to further support a larger double blinded placebo control trial.

2.4. Statistical analysis

The primary outcome measure will be changes in the mean total 21-item DRSP score during the luteal phase of the control cycles compared to the mean total 21-item DRSP score during the luteal phase of the treatment cycles. This will involve conducting two repeated measures, one sample t-tests. The first will compare the mean DRSP score across the two-weeks prior to the end of the first cycle (Cycle One: First Control Cycle, week three and four) to the mean DRSP score across the two-weeks prior to the end of the first treatment cycle (Cycle Three: First Treatment Cycle, week 11 and 12) (Fig. 1, Table 4). This will be repeated for the mean DRSP score across the luteal phase of the second control cycle (Cycle Two: Second Control Cycle, week seven and eight) compared to the second treatment cycle (Cycle Four: Second Treatment Cycle, week fifteen and sixteen) (Fig. 1, Table 4). The aim is to compare the differences in DRSP scores, including items assessing mood and physical symptoms, alongside social impacts of these symptoms, in the luteal phase of the control and treatment cycles. This study is likely to detect preliminary effect sizes with differences in DRSP scores being the primary outcome. As such, a Bonferroni correction will be applied to correct for type I error during statistical analysis. Effect size will be calculated using Cohen's 'd' approximation. Previous studies have demonstrated a statistically significant decreases in total DRSP score of 75% in treatment groups compared to 47% in the placebo group with an effect size of d = 0.7 [70]. A similar effect size will be targeted for the primary outcome.

The secondary outcome measure will include the total DASS-21 score over the past 14-days as a repeated single survey at the end of each cycle. Statistical analysis will involve a comparison of the total DASS-21 score recorded at the end of the control cycles compared to the treatment cycles. This will involve conducting two repeated measures, one sample t-tests. The first will compare the total DASS-21 score recorded at the end of the first control cycle (Cycle One: First Control Cycle, end of week four), compared to the total DASS-21 score recorded at the end of the first treatment cycle (Cycle Three: First Treatment Cycle, end of week 12) (Fig. 1, Table 4). The second will compare the total DASS-21 score recorded at the end of the second control cycle (Cycle Two: Second Control Cycle, end of week eight), compared to the total DASS-21 score recorded at the end of the second treatment cycle (Cycle Four: Second Treatment Cycle, end of week 16) (Fig. 1, Table 4). The aim of DASS-21 comparison is to assess differences in mood symptoms, including depression, anxiety, and stress. Effect size will be measured by comparing DASS-21 scores in control cycles compared to treatments. In previous studies reductions in DASS-21 scores have been demonstrated with an effect size of d = 0.86 of hormonal therapy compared to placebo [71]. A similar effect size will be targeted.

2.5. Ethical considerations

Ethics approval to conduct the proposed research study detailed in this protocol has been obtained by the Monash Research Ethics Committee. Participants will be recruited through local mental health service social media platforms (Facebook and Twitter), alongside written advertisements placed in a community mental health clinic. Participants will be screened for eligibility via telephone. Informed consent will be obtained prior to implementation of any elements of the study protocol. Participants will be sent a copy of the Participant Information and Consent Form (PICF) prior to the informed consent discussion. Participants will be able to sign the informed consent form electronically.

SAMe 400 Complex is registered as a CAM in Australia and The United States. Side effects are detailed above, and appear to be dose-dependent, with stomach cramps and fluid retention observed in doses up to 3200 mg, nearly three times to proposed dosage in the current study [53,54]. The contraindications to SAMe are described above, including BPAD and pregnancy, or concurrent psychotropic treatment (namely, SSRIs or the alike). To ensure an adequate wash-out period from previous psychotropic agent use (particularly SSRIs or SNRIs), a four-week period of non-treatment is required to be eligible for participation [64].

SAMe 400 Complex will be administered in a formulation with other active ingredients including cyanocobalamin, folic acid, pyridoxine hydrochloride, riboflavin and zinc amino acid chelate. As this product contains vitamin B6, participants should cease SAMe 400 Complex if experiencing the sensations of numbness, tingling, or burning sensations, seek advice from a healthcare practitioner, and alert research staff. Participants are encouraged to disclose both prescription and non-

prescription medications they may be taking.

The proposed study will conduct safety monitoring and reporting as per the National Health and Medical Research Council (NHMRC) Safety National Statement on Ethical Conduct in Human Research 2023 [72]. Adverse events will be recorded using the SAE questionnaire. Responses to the SAEs will be monitored rigorously and regularly reviewed by research staff. Research staff will also be notified of any SAE responses reported by participants under the 'severe' category. This will prompt the primary investigator to contact the participant to discuss the adverse events further. Adverse events will be reported immediately to the participants treating doctor if the participant has provided their details and have consented to this. The proposed study is to be conducted remotely, using online questionnaires and postal mailing services.

3. Concluding remarks

PMDs are highly prevalent disorders with debilitating symptomology. There are limited treatment options for those who don't respond to first line-treatments, for those who current treatments are contra-indicated, or for individuals who preference alternative therapies. SAMe 400 Complex is a CAM with emerging roles in the treatment of depression, which may be used intermittently throughout the menstrual cycle to alleviate somatic and psychological symptoms as a novel treatment for PMDs. The proposed study aims to explore preliminary treatment effects of SAMe 400 Complex in individual's with PMDs in a within study measures design pilot study. It is hypothesised that SAMe treatment will reduce the overall severity of PMDs symptoms as measured by the DRSP questionnaire in treatment menstrual cycles compared to control menstrual cycles. Secondary measures of SAMe effects on anxiety and depression in PMDs will be explored using the DASS-21. The proposed study will explore the feasibility of recruitment, participant retainment and SAMe tolerability (as determined by the SAEs). This study aims to provide justification for a larger randomised control trials, including placebo controls and comparisons to gold-standard treatments such as SSRIs. Publication of these research findings will contribute to the body of knowledge surrounding PMDs and their treatment.

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CRediT authorship contribution statement

Brendan Stevenson: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Emorfia Gavrilidis:** Writing – review & editing, Project administration, Methodology, Investigation, Funding acquisition, Data curation. **Yasmin Malik:** Project administration, Investigation. **Jayashri Kulkarni:** Writing – review & editing, Resources, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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