L-theanine in the adjunctive treatment of generalized anxiety disorder: A double-blind, randomised, placebo-controlled trial

Jerome Sarris\(^a, b, \ast\), Gerard J. Byrne\(^c\), Lachlan Cribb\(^b\), Georgina Oliver\(^b\), Jenifer Murphy\(^b\), Patricia Macdonald\(^c\), Sonia Nazareth\(^c\), Diana Karamacoska\(^a\), Samantha Galea\(^b\), Anika Short\(^c\), Carolyn Ee\(^a\), Yoann Birling\(^a\), Ranjit Menon\(^b\), Chee H. Ng\(^b\)

\(^a\) NICM Health Research Institute, Western Sydney University, Westmead, NSW, Australia
\(^b\) The Professorial Unit, The Melbourne Clinic, Department of Psychiatry, The University of Melbourne, Richmond, VIC, Australia
\(^c\) The University of Queensland, Faculty of Medicine, Discipline of Psychiatry, Herston, QLD, Australia

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**ABSTRACT**

Partial or non-response to antidepressants in Generalized Anxiety Disorder (GAD) is common in clinical settings, and adjunctive biological interventions may be required. Adjunctive herbal and nutraceutical treatments are a novel and promising treatment option. L-theanine is a non-protein amino acid derived most-commonly from tea (Camellia sinensis) leaves, which may be beneficial in the treatment of anxiety and sleep disturbance as suggested by preliminary evidence. We conducted a 10-week study (consisting of an 8-week double-blind placebo-controlled period, and 1-week pre-study and 2-week post-study single-blinded observational periods) involving 46 participants with a DSM-5 diagnosis of GAD. Participants received adjunctive L-theanine (450–900 mg) or matching placebo with their current stable antidepressant treatment, and were assessed on anxiety, sleep quality, and cognition outcomes. Results revealed that adjunctive L-theanine did not outperform placebo for anxiety reduction on the HAMA (p = 0.73) nor in insomnia severity on the Insomnia Severity Index (ISI; p = 0.35). However, LT treated participants reported greater self-reported sleep satisfaction than placebo (ISI item 4; p = 0.015). Further, a separation in favour of L-theanine was noted on the ISI in those with non-clinical levels of insomnia symptoms (ISI ≤ 14; p = 0.007). No significant cognitive effects (trail making time and the modified emotional Stroop) were revealed. While this preliminary study did not support the efficacy of L-theanine in the treatment of anxiety symptoms in GAD, further studies to explore the application of L-theanine in sleep disturbance are warranted.

**1. Introduction**

Effective first-line treatments for Generalized Anxiety Disorder (GAD) include psychotherapy such as Cognitive Behavioural Therapy (Carpenter et al., 2018) and pharmacotherapies such as antidepressants and anxiolytic agents (Reinhold and Rickels, 2015). With antidepressant treatments, the remission rates are typically in the realm of 30–50% (Reinhold et al., 2011). As such, adjunctive agents (such as benzodiazepines, pregabalin and/or antipsychotics) are often used to enhance the effectiveness of antidepressants in those who are non-responsive (Latas et al., 2018). A common co-occurrence with GAD is insomnia (Ferre Navarrete et al., 2017), and subjectively reported sleep disturbance is an important part of GAD symptomology (Cox and Olatunji, 2016). Nutraceuticals and ‘phytoceuticals’, pharmaceutical grade nutrients or plant-based compounds with bioactive effects, are increasingly being considered as novel adjunctive options in psychiatric disorders, due to their potential efficacy and acceptable tolerability (Sarris et al., 2016, 2010).

L-theanine (n-ethylglutamic acid; LT) is a non-proteinogenic amino acid derived almost exclusively from tea leaves (Camellia sinensis), with the highest concentrations found in green, oolong, and Pu-erh tea (Syu et al., 2008). A natural ethylamide analogue of glutamate, preclinical studies have found LT to pass freely through the blood-brain barrier, reduce presynaptic glutamate release (Kakuda et al., 2008), increase inhibitory neurotransmitter GABA, and enhance glycine and dopaminergic release (Kakuda et al., 2008; Kimura and Murata, 1971; Shen et al., 2011; Yamada et al., 2007, 2005). Although the direct effects of LT on GABA pathways is not well understood, a recent study has shown differential decreases of cortical and hippocampal GABA in mouse models (Schallier et al., 2013). A comprehensive review of LT's...
neuropharmacology has also highlighted its neuroprotective effects, as well as the ability to increase alpha wave brain activity (Lardner, 2014). Alpha brain-activity is a measure of wakeful relaxation and has been associated with creativity, improved concentration, and decreased anxiety (Lardner, 2014). Owing to its influence on inhibitory neurotransmission, as well as promotion of alpha brain wave activity, LT has been investigated in animal models of anxiety, demonstrating anxiolytic as well as antidepressant activity (Ogawa et al., 2018; Unno et al., 2013a; Wakabayashi et al., 2012).

While preclinical and clinical evidence (covered in the Discussion) suggests that LT has anxiolytic and hypnotic properties, clinical trials investigating its therapeutic effects in anxiety disorders are lacking. Further, there is a deficit of augmentation studies in GAD, and no studies have investigated the potential usefulness of different doses of LT. Thus our current study aimed to elucidate the efficacy and safety of adjunctive LT in the treatment of GAD, with an a priori hypothesis that the compound would reduce participant’s anxiety and insomnia severity. An additional aim was to assess whether a titrated high dose of LT (900 mg/day) is needed in cases of non-response to the initial 450 mg/day dose.

2. Methods

2.1. Overview

This was a phase II, randomised, double-blind, placebo controlled, multi-centre pilot study comparing adjunctive LT to adjunctive placebo in individuals with GAD who were non-responsive to their current antidepressant. The study was conducted between 2016 and 2018 and study sites were located in Australia at The Melbourne Clinic (Richmond, Melbourne), The Royal Brisbane and Womens Hospital (Herston, Brisbane) and NICM Health Research Institute (Campbelltown, New South Wales). The trial was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR # 12616000759493) on 9th June 2016, and Human Research Ethics Committee approvals obtained from each trial site to conduct the study (TMCREC 273; UQ MREC 2016000774; WSU HREC H12268).

2.2. Eligibility criteria

Eligible participants met the following criteria: aged between 18 and 75 years; primary diagnosis of GAD at study entry (DSM-5; confirmed via the MINI International Neuropsychiatric Interview version 6.0 (MINI 6.0) and Hamilton Anxiety Rating Scale (HAMA) score ≥16); taking an antidepressant medication at a stable dose for minimum four-weeks at a therapeutic dose for GAD. Women were required to use adequate contraception throughout the study period.

Participants were excluded if they were experiencing a current episode of depression (as per MINI 6.0 or ≥18 Montgomery-Asberg Depression Scale [MADRS] score); diagnosis of Bipolar or Psychotic Disorder/s (self-reported by the participant, as per their treating doctor, or as per MINI 6.0); current alcohol or substance abuse (as per MINI 6.0); recently commenced psychotherapy (acceptable if stable for more than four weeks); known or suspected clinically unstable medical conditions; consummation of more than three cups of tea per day (due to presence of LT in tea); presenting with suicidal ideation at baseline (> 3 on MADRS suicidal thoughts domain); three or more failed antidepressant trials for the current episode of GAD; pregnancy or breastfeeding. Participants were withdrawn from the study if they: elected to change their current antidepressant or psychotherapy program; initiated new treatment/s outside the study protocol; had a MADRS score > 23 at any time point after baseline; ceased adequate contraception methods or fell pregnant; experienced a serious adverse event or newly diagnosed medical conditions which the medical investigator/s deemed necessary for them to withdraw.

2.3. Measures

Due to the two major hypothesis-driven clinical areas of inquiry (anxiety and insomnia), we used dual primary outcome measures: the Hamilton Anxiety Rating Scale (HAMA) was administered according to the Structured Interview Guide for the Hamilton Anxiety Scale (SIGHA) for the anxiety outcome (Hamilton, 1959), and the Insomnia Severity Index (ISI) for the insomnia outcome (Morin et al., 2011). Secondary outcome measures included the MADRS (Montgomery and Asberg, 1979), a clinician reported measure of depression severity, the Beck Anxiety Inventory (BAI) (Beck et al., 1988), Penn State Worry Questionnaire (PSWQ) (Meyer et al., 1990) and World Health Organisation Quality of Life-BREF (WHOQOL-BREF) (The WHOQOL GROUP, 1998). A trail making task (measuring time in seconds to complete task) was used to determine the effect of LT on cognition. A modified emotional Stroop task was also undertaken in which participant’s response times to name colours of positive, neutral and anxiety-related words (such as stroke, debts, crazy) was measured. The self-reported Systematic Assessment for Treatment Emergent Effects (SAFTEE) was used to assess for the presence and severity of adverse events (Levine and Schooler, 1986). The WHOQOL-BREF, trail making time and the modified emotional Stroop were completed at baseline and Week-8. All other measures were completed at each time point.

2.4. Treatment intervention

Eligible participants were initially randomised, via independent computer-generated block randomisation to receive, in addition to their current antidepressant, LT at 450 mg per day (given as one 225 mg capsule twice per day, or placebo matched for appearance, taste, and scent) for the first four weeks of the study. Participants who did not achieve a ≥35% reduction in their baseline HAMA score at Week-4 were titrated to two capsules, twice per day (900 mg LT per day, or matching placebo) for the remaining four weeks of the treatment intervention phase. Titration at Week-4 is in line with flexible dosing seen in clinical practice where some patients, due to individual pharmacokinetic and pharmacodynamic differences, require a higher dose to achieve response. Participants ceased taking capsules for the last two weeks of the study (from Week-8 to Week-10) which was used to monitor for any potential ongoing therapeutic activity or withdrawal effect from the LT.

2.5. Procedures

The study was advertised via social media, on anxiety support group webpages and outpatient clinics (e.g. flyers distributed in psychology and GP clinics). Enquiring individuals were initially telephone screened by psychology or mental health qualified research staff to determine if basic criteria were met. If so, they were invited to attend a baseline screening session where informed consent was obtained. Demographics, MINI 6.0 (for psychiatric diagnoses) and medical history were then assessed, and outcome assessments were conducted. At Week-1, a phone interview was conducted where the HAMA was administered to determine persistence of anxiety symptoms. If the participant remained eligible (HAMA ≥16 and ≤35% reduction in HAMA score), their allocated treatment was posted (containing 30 capsules) with written dosage instructions. Participants were instructed to take one capsule (two if titrated from Week-4 onwards) in the morning and one capsule (two if titrated from Week-4 onwards) in the afternoon/early evening. Dose instructions to participants were nonspecific as to whether to take the capsules with food. Participants attended follow-up visits at Week-2, 4, 6 and 8 where the HAMA, MADRS, BAI, PSWQ, ISI, and SAFTEE were completed (WHOQOL-BREF, cognition and modified Stroop assessments were also completed at Week-8). Drug use, alcohol, caffeine and tea consumption was also recorded at each visit. At Week-10 (conducted two weeks after IP washout) only the HAMA, MADRS and
SAFTEE were completed. Additional capsules were dispensed each fortnight (30–60 capsules, depending on titration schedule) and participants were asked to return any remaining capsules at each follow-up visit to determine compliance. Participants were reimbursed $10 in the form of department/food store gift vouchers for each appointment visit they attended (to cover travel expenses).

2.6. Statistical analysis

Sociodemographic variables were tested for between-group differences using t-tests for continuous variables and Chi-squared tests for categorical variables. Primary and secondary measures were assessed for change across time utilising Linear Mixed effects Models (LMMs). LMMs included main effects of Time, Group and a Group × Time interaction. A random effect of subject (Site x Participant) and random intercept was also included. A random slope was included depending on results of the Wald test and Bayesian Information Criterion (BIC). Covariance structure was chosen based on visual inspection of the data and inspection of BIC. Models are presented unadjusted unless clearly stated. Adjusted models included covariates such as trialsite, titration, age, gender, current treatments and caffeine intake. Only covariates which had significant main effects were retained in adjusted models. Primary analysis of the data was conducted with blinding to group allocation. Tests of significance were conducted using a two-sided alpha of 0.05. Data was analysed using the Statistical Package for Social Sciences software (SPSS, version 24.0, IBM, Chicago).

3. Results

3.1. Sample and participant characteristics

After screening and baseline exclusions (Fig. 1), a total sample size of 46 participants was available for analysis. There were 19 participants who completed the Week-9 visit (86.4%) in the active group, compared to 18 (73.9%) in the placebo group (35%). For the HAMA, participant’s data was excluded due to treatment non-adherence and another participant had their Week-8 data excluded, also due to non-adherence (< 60% adherence). The remaining participants in the study (n = 44) achieved at least 70% adherence based on returned capsule counts. Finally, data collected subsequent to Week-4 was removed from two participants due to protocol deviations (change of antidepressant and starting psychotherapy, respectively).

Demographic and clinical characteristics of the full sample are displayed in Table 1. Concurrent psychotherapy was significantly more frequent in the LT group (73%) than the placebo group (35%), χ²(1,45) = 6.51, p = 0.011. The mean age was significantly higher in the LT group (40.7 ± 15.0) than in the placebo group (32.2 ± 9.29), t (1,43) = −2.26, p = 0.029 (See. Figs. 2 and 3).

3.2. Primary outcomes (anxiety and insomnia)

Baseline and change scores for primary and secondary models are displayed in Table 2. Groups were matched on each measure except for the BAI, in which self-reported anxiety was more severe in the LT group (25.00 ± 9.58) than the placebo group (20.3 ± 9.11), with a trend towards significance, t(40) = −1.73, p = 0.092. On the HAMA, a significant effect for Time was revealed, indicating an overall reduction in anxiety across time in the pooled sample, F(1,162) = 44.2, p < 0.001. However, a non-significant Group × Time interaction indicated no significant additional effect of LT treatment, F(1,162) = 0.78, p = 0.38. In adjusted models, none of the investigated covariates altered this relationship or demonstrated an interaction with Group and/or Time. No change in anxiety was found when LT administration was ceased when comparing endpoint HAMA score (Week 8; 14.59 ± 6.00) to post washout HAMA score (Week 10; 14.00 ± 5.71) in the LT group only, t (16) = −0.34, p = 0.74.

On the ISI, a non-significant trend for Time on LMMs suggested improvement over time in the pooled sample, F(1,162) = 3.11, p = 0.084. Subsequent to Week-2, the LT group showed lower insomnia symptoms relative to the placebo group at each visit, although this was not reflected in a significant Group × Time interaction, F(1,52) = 0.90, p = 0.35. Considering only participants with ‘clinical insomnia’ (baseline ISI score > 14; n = 18), there was similarly no significant treatment-effect noted, F(1,64) = 2.17, p = 0.15. However, in patients who did not meet criteria for clinical insomnia (baseline ISI score ≤ 14; n = 25), a significant treatment-effect was noted in favour of LT, F (1,84) = 7.52, p = 0.007. No correlation between change in HAMA score and change in ISI score was noted in the LT group, indicating that any benefit to sleep was not secondary to reduced anxiety (r = 0.174, p = 0.49). Finally, in the LT group alone, change in ISI score was significantly correlated with HAMA score at baseline (r = −0.51, p = 0.031), indicating that response on the ISI may depend on baseline anxiety severity.

Each of the items of the ISI were investigated individually to further investigate the role of LT in insomnia. A significant treatment effect was found only for item 4 “How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?”, in which LT significantly improved subjective sleep satisfaction, F(1,154) = 6.08, p = 0.015. Further, considering only participants without clinical insomnia (baseline ISI score ≤ 14), significant treatment effects in favour of LT were found for item 1 “Difficulty falling asleep” (p = 0.049), item 3 “Problems waking up too early” (p = 0.017), item 4 (p < 0.001) and item 7 “To what extent do you consider your sleep problem to INTERFERE with your daily functioning” (p = 0.030).

3.3. Secondary outcomes

The Group × Time interaction on the MADRS (F(1,84) = 0.817, p = 0.37), BAI (F(1153) = 0.815, p = 0.37) and the PSWQ (F (1152) = 0.010, p = 0.92) were found to be non-significant. Trail making time, as well as neutral, positive and anxiety card completion time on the modified emotional Stroop also showed no separation between groups (data not shown; all p > 0.05). After adjusting for covariates, results remained unchanged in each model. Finally, there was no evidence that caffeine intake interacted with LT treatment in any of the assessed measures.

3.4. Titration

The proportion of participants who were titrated did not differ between the LT group (n = 9; 40.9%) and the placebo group (n = 9; 39.1%), results NS. On the HAMA, participants titrated in the LT group had a higher baseline (Week 0) to endpoint (Week 8) change score (−5.89 ± 4.76) compared to participants not titrated (−3.92 ± 6.75). However, this effect was non-significant, F(1,20) = 0.57, p = 0.46. Excluding participants who were titrated did not markedly alter results of the above LMMs for the HAMA, ISI, BAI, MADRS, or scores on the trail making test and emotional Stroop.

3.5. Adverse events (AEs)

There was no significant difference in AEs (measured on the SAFTEE) between placebo and LT groups, t(41) = 0.32, p = 0.75. The most commonly reported adverse events on the SAFTEE were sleep disturbance (active = 11, placebo = 15), drowsiness (active = 11, placebo = 11), weakness/fatigue (active = 9, placebo = 13), irritability (active = 9, placebo = 11), trouble concentrating (active = 7, placebo = 11) and gastrointestinal discomfort (active = 7, placebo = 10). No adverse events were significantly more common in either group. After incorporating SAFTEE severity scores of each item (measured on a scale of 1–4), however, the placebo group reported significantly worse sleep disturbance as an adverse event than LT, t
There were no differences in reported adverse events between LT participants who were titrated and those who were not.

4. Discussion

To our knowledge this was the first study investigating the use of adjunctive L-theanine in the treatment of anxiety and sleep disturbance in GAD. While LT did not demonstrate any beneficial effect over placebo on measures of anxiety, mood, worry or cognition, there was indication that LT may improve self-reported sleep satisfaction in GAD, and insomnia symptoms overall in a subset of individuals with GAD.

This tentative association was supported by a significant treatment effect of LT on the sleep satisfaction item of the ISI, as well as a significant Group × Time interaction in individuals who did not meet threshold criteria for clinical insomnia (as described by the ISI). As such, LT may have a particular benefit in improving sleep in individuals with mild insomnia symptoms. The efficacy of LT in insomnia was also supported by more severe ‘sleep disturbance’ recorded as an adverse event in the placebo group relative to LT. It is noted, however, that no separation by treatment was observed in the analysis of the complete sample on the ISI and that subgroup analyses of such modest sample size (n = 25), are susceptible to type II error (although the observed p value did indicate a highly significant interaction). As no correlation between change in ISI score and change in HAMA score across the trial was noted in the LT group, this effect of LT does not appear to be secondary to any effect on anxiety. However, individuals who had lower baseline HAMA scores were more responsive on the ISI, indicating that response may also depend on baseline anxiety severity. As such, LT may potentially have been efficacious in improving mild insomnia symptoms as these symptoms are relatively less entangled with severe symptoms of anxiety. Interestingly, this suggests that LT may offer similar (or potentially greater) efficacy in non-anxious populations experiencing insomnia (particularly of sub-clinical severity). This potentiality is also...
highlighted by recent developments in insomnia research which suggest that insomnia should not be considered a 'primary' or 'secondary' disorder as such, as little evidence suggests that insomnia comorbid with psychiatric illness is qualitatively different to that which is not (Stepeński and Rybarczyk, 2006).

Observed results are supported by a previous RCT in 93 children which demonstrated an LT related improvement to sleep quality (not observed on parent-reported sleep reports) (Lyon et al., 2011), as well as an open label trial which demonstrated improvement in PSQI scores in 20 participants with MDD (Hidese et al., 2016). A further open label study in 17 patients with schizophrenia has reported improvements in subjective sleep quality (as per the PSQI) after 8-week of LT (250 mg/day) supplementation (Ota et al., 2015). Additionally, LT has been shown to partially reverse the effects of caffeine-induced sleep disturbance in a rat model, providing further evidence for LT's therapeutic potential in insomnia (Jang et al., 2012).

Anxiolytic and anti-stress effects of LT have been reported in a non-clinical population of pharmacy students (Unno et al., 2013b), and an open label (n = 20) depression study (250 mg/day adjunctive to antidepressants) (Hidese et al., 2016). Further, a 2-week RCT (n = 60) investigation of LT in schizophrenia (400 mg/day, adjunctive to antipsychotics) found significant anxiolytic effects, although it is uncertain whether the separation observed in this study was more related to differences in baseline score than response to treatment (as response slopes show little observable separation; and the data is not clearly reported) (Ritsner et al., 2011). The current study did not replicate these previous, positive findings. While LT may be an efficacious treatment option in sub-clinical anxiety, or anxiety which is secondary to other conditions, as previous studies have reported, our study has found lack of benefit in primary GAD. This is in line with the findings of Lu et al. (2004) who failed to find an acute effect of LT on anticipatory anxiety when compared to alprazolam and a placebo.

Overall, LT was very well tolerated, with no serious adverse events noted. It is however worth noting that there is evidence suggesting the therapeutic effects of LT reaches a plateau at 400 mg/day, whereas our study had titrated the dose up to 900 mg/day. One particular study found the use of LT at 200 mg/day and 400 mg/day, but not 600 mg/day, increased sensorimotor gating in 14 healthy controls (Ota et al., 2014). Sensorimotor gating is thought to be disrupted in certain psychiatric disorders such as anxiety and schizophrenia and is the process of filtering unnecessary stimuli in the brain (Ota et al., 2014). Further, the Jang et al. (2012) rat model found low doses of LT, not higher doses, counteracted the effects of caffeine-induced sleep disturbance. These findings need to be considered with caution, as they were conducted in small, non-clinical and animal samples and this may not be generalisable to our clinical study population. In the current study, patients who were titrated to a doubled dose of LT (900 mg/day) were no more likely to experience adverse events than those who were not titrated. They also had a higher baseline to endpoint change score compared to the participants not titrated, albeit this effect was non-significant. This suggests that a higher dose of 900 mg/day may improve the response for some participants such as, in cases of non-response. It is also worth considering that a longer duration at 450 mg/day may have shown a treatment effect and optimal dosing should be investigated in future studies.

Several strengths of this study are noted, including its double-blind, placebo-controlled design, thoroughly considered and implemented inclusion and exclusion criteria, and the use of a non-treatment one week 'run-in' period. A modest sample size is however recognized as a limitation. Secondly, pertinent covariates, such as type, and dose of antidepressant could not be adequately investigated for due to limitations in statistical power. The significant difference in psychotherapy treatment between the two groups may have had an impact on outcomes, with the LT group potentially being more challenging to treat (due to non-response to both antidepressant and psychological therapy, and a higher mean age). Finally, we acknowledge the lack of objective measurement of sleep as an additional limitation of the study, and suggest the use of actigraphy or polysomnography, as appropriate, to explore the effect of LT on objective sleep parameters in further studies.
Finally, it is worth noting that the non-specific dosing instructions provided to participants, may have created pharmacokinetic variations depending on whether the LT was taken with or away from food or beverages.

In conclusion, while this preliminary pilot study found no evidence to support the efficacy of adjunctive LT in the treatment of anxiety in GAD, LT may improve sleep satisfaction, as well as symptoms of sleep disturbance in cases of mild insomnia. A larger study focusing on insomnia as the primary outcome is required to validate this finding.

Conflicts of interest

J. Sarris has received either presentation honoraria, travel support, clinical trial grants, book royalties, or independent consultancy payments from: Integria Healthcare & MediHerb, Pfizer, Scius Health, Key Pharmaceuticals, Taki Mai, FIT-BioCeuticals, Blackmores, Soho-Flordis, Healthworld, HealthEd, HealthMasters, Kantar Consulting, Research Reviews, Elsevier, Chaminade University, International Society for Affective Disorders, Complementary Medicines Australia, SPRIM, Terry White Chemists, ANS, Society for Medicinal Plant and Natural Product Research, Sanofi-Aventis, Omega-3 Centre, the National Health and Medical Research Council, CR Roper Fellowship.

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Table 2

<table>
<thead>
<tr>
<th>Measure</th>
<th>Baseline, mean (SD)</th>
<th>End point (week 8), mean (95% CI)</th>
<th>Statistic1</th>
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<td></td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
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<tr>
<td>HAMA</td>
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<td>21.9 (4.01)</td>
<td>14.3 (11.6, 16.9)</td>
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<tr>
<td>MADRS</td>
<td>11.9 (3.86)</td>
<td>12.9 (2.85)</td>
<td>9.17 (6.86, 11.5)</td>
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<tr>
<td>PSWQ</td>
<td>62.8 (12.2)</td>
<td>63.0 (10.5)</td>
<td>57.6 (52.4, 62.8)</td>
</tr>
<tr>
<td>BAI</td>
<td>20.3 (9.11)</td>
<td>25.3 (9.58)</td>
<td>10.9 (7.17, 14.6)</td>
</tr>
<tr>
<td>ISI</td>
<td>10.7 (9.12)</td>
<td>11.7 (6.05)</td>
<td>10.6 (7.66, 13.5)</td>
</tr>
</tbody>
</table>

HAMA – Hamilton Anxiety Rating Scale; MADRS – Montgomery-Asberg Depression Rating Scale; PSWQ – Penn State Worry Questionnaire; BAI – Beck Anxiety Inventory; ISI – Insomnia Severity Index; *Estimated marginal means derived from LMM; 1Group × Time interaction effect from linear mixed effects model.
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CredIt authorship contribution statement

Jerome Sarris: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing – original draft, Writing – review & editing. Gerard J. Byrne: Investigation, Project administration, Resources, Supervision, Writing – review & editing. Laachlan Cribb: Formal analysis, Methodology, Writing – review & editing. Georgina Oliver: Methodology, Project administration, Writing – review & editing. Jenifer Murphy: Formal analysis, Methodology, Project administration, Writing – review & editing. Patricia Macdonald: Project administration. Sonia Nazareth: Project administration. Diana Karamacoska: Project administration. Samantha Galea: Project administration. Anika Short: Project administration. Carolyn Ee: Data curation, Investigation, Resources, Writing – review & editing. Yoann Birling: Writing – review & editing. Ranjit Menon: Investigation, Supervision. Chee H. Ng: Investigation, Resources, Supervision, Writing – review & editing.

Samantha Galea: Project administration. Anika Short: Project administration.

Patricia Macdonald: Project administration.

Yoann Birling: Writing – original draft.

Methodology, Project administration.

Samantha Galea: Project administration.

Jenifer Murphy: Writing – original draft.

Methodology, Project administration, Writing – review & editing.


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