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An open-label pilot study of combined augmentation with creatine monohydrate and 5-hydroxytryptophan for SSRI- or SNRI-resistant depression in adult women

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Abstract

Purpose—Many women with major depressive disorder (MDD) respond inadequately to standard treatments. Augmentation of conventional antidepressants with creatine monohydrate and 5-hydroxytryptophan (5-HTP) could correct deficits in serotonin production and brain bioenergetics associated with depression in women, yielding synergistic benefit. We describe an open-label study of 5-HTP and creatine augmentation in women with MDD who had failed selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) monotherapy.

Methods—15 women who were adequately adherent to an SSRI or SNRI and currently suffering from MDD, with a 17-item Hamilton Depression Rating Scale (HAM-D) score ≥ 16, were treated with 5g of creatine monohydrate daily and 100mg of 5-HTP twice daily for 8 weeks, with 4 weeks of post-treatment follow-up. The primary outcome was change in mean HAM-D scores.

Results—Mean HAM-D scores declined from 18.9 ± 2.5 at pretreatment visits to 7.5 ±4.4 ($p < 0.00001$), a decrease of 60%. Participants did not experience any serious treatment-related adverse events.

Conclusions—Combination treatment with creatine and 5-HTP may represent an effective augmentation strategy for women with SSRI- or SNRI-resistant depression. Given the limitations of this small, open-label trial, future study in randomized, placebo-controlled trials is warranted.

Keywords

major depressive disorder; altitude; hypobaric hypoxia; serotonin; brain bioenergetics

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1. Introduction

Major depressive disorder (MDD) is a chronic illness with a lifetime prevalence of over 16%.[1] It is associated with significant personal and social costs,[2] diminished quality of life, and disability.[3,4] This burden falls disproportionately on women. They are twice as likely as men to develop depression,[5] are more likely to attempt suicide[6] and to take antidepressants,[7] and are overrepresented in clinical trials of treatment-resistant depression.[8] Accordingly, studies addressing the treatment of depression in women and the development of treatment-resistance are urgently needed.

The mechanisms underpinning the higher rates of depression in women are not known and many possibilities have been suggested. One possibility involves alterations in serotoninergic pathways, which are often associated with depression and suicide.[9] Women may be more vulnerable to processes that impair serotonin production, since women exhibit lower baseline serotonin levels.[10] Conversely, women may be more responsive to serotonin replacement strategies. Although selective serotonin reuptake inhibitors (SSRIs) are widely prescribed for MDD, animal studies suggest that they may be less effective in the setting of reduced serotonin synthesis, as SSRI non-response is observed in several serotonin depletion paradigms.[11–13] Deficits in serotonin synthesis could be corrected by supplementation with 5-hydroxytryptophan (5-HTP),[14] which is metabolized directly into serotonin by l-aromatic acid decarboxylase.[15] 5-HTP has previously been investigated as an antidepressant, increases brain serotonin stores when administered orally,[15,16] and increases extracellular serotonin levels in mice deficient in tryptophan hydroxylase or receiving a serotonin reuptake inhibitor.[17] To our knowledge, 5-HTP has not been investigated as an augmenting agent for use with SSRIs or SNRIs in humans, probably because of concerns about serotonin syndrome,[18] though it has been successfully combined with tricyclic antidepressants[19–21] and monoamine oxidase inhibitors.[22]

Inadequate response to traditional antidepressants could also result from alterations in brain bioenergetics. In depressed adults, phosphorus magnetic resonance spectroscopy demonstrates reduced total nucleotide triphosphate concentrations and higher phosphocreatine concentrations when compared to healthy volunteers, and this pattern is more common in women.[23–25] These changes can be rectified by administration of oral creatine monohydrate, which is also emerging as an effective augmenting agent for depression. In human trials involving women, oral creatine alters brain creatine, phosphocreatine, and total nucleotide triphosphate levels[26,27] in tandem with improvements in mood.[28] In a large placebo-controlled study, creatine augmentation of escitalopram produced significant improvements in depression scores compared to placebo in treatment-naïve women with MDD.[29]

Because of the increased vulnerability of women to depression, and because women may be more responsive to both creatine supplementation and correction of serotonin deficits than men, we undertook a pilot open-label study to examine the combined use of creatine and 5-HTP as augmenting agents for the treatment of depression in women with incomplete responses to SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs). Combined treatment was utilized in the hope that the two supplements would have synergistic efficacy.

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2. Materials and Methods

2.1 Subject Selection

Adult women with MDD confirmed by the Structured Clinical Interview for DSM-IV were recruited. Subjects were required to have continued depression of at least moderate severity at both the screening and baseline visits, with 17-item Hamilton Depression Rating Scale (HAM-D) scores ≥ 16, despite adequate adherence to at least 8 weeks of any Food and Drug Administration-approved SSRI or SNRI at standard doses. Eligible dose ranges for antidepressants represented in the study included citalopram 20mg-40mg daily,[30] escitalopram 10mg-20mg daily,[31] fluoxetine 20mg-80mg daily,[32] fluvoxamine 100mg-300mg daily,[33] sertraline 50mg-200mg daily,[34] paroxetine 20mg-50mg daily,[35] venlafaxine 75mg-375mg daily,[36,37] and duloxetine 40mg-120mg daily.[38] We assessed whether subjects had received an adequate trial of their current antidepressant based on Antidepressant Treatment Response Questionnaire (ATRQ) dosage guidelines.[39] Adherence was assessed by participant report and required completion of at least 75% of scheduled doses. Exclusion criteria included histories of bipolar disorder, psychotic illness, renal disease, diabetes, colitis or diverticulitis, pulmonary disease, cardiac disease, corrected QT interval > 500ms, seizure disorder, current serious suicide risk identified by the Columbia Suicide Severity Rating Scale (C-SSRS), current treatment with an antipsychotic, mood stabilizer, neurostimulation, or any non-SSRI/SNRI antidepressant, and pregnancy. Because of the possible increased risk of serotonin syndrome in subjects taking an SSRI/SNRI and 5-HTP, subjects with a history of serotonin syndrome were excluded. Because of an association between tryptophan and eosinophilia-myalgia syndrome (EMS), subjects with rheumatologic conditions, a history of tryptophan intolerance, or pre-existing eosinophilia were excluded. The study was approved by the local institutional review board, and informed consent was obtained from all participants. The trial was registered with ClinicalTrials.gov (identifier: NCT02356107).

2.2 Study Measures and Intervention

This open-label study of 5-HTP and creatine as combined augmentation treatment included a 2-visit screening phase to assure eligibility, an 8-week treatment phase with visits at weeks 1, 2, 4, 6, and 8, and two post-treatment visits at weeks 10 and 12. Participants were given fixed-doses of 5g of Creapure® brand of Creatine (AlzChem LLC, Trostberg, Germany) and 100 mg twice daily of 5-HTP derived from *Griffonia* seed extract (Fuller Enterprise USA Inc, Ontario, Canada) by mouth daily for 8 weeks, in addition to their usual dose of SSRI or SNRI. Vital signs and a screening physical were performed at each visit. Adverse events were assessed at each visit, and subjects were asked about 5-HTP-specific effects such as nausea, vomiting, diarrhea, insomnia, palpitations, headache, and weight gain.[40] No specific inquiries were made regarding adverse effects of creatine, as generally these are negligible.[41,42] Study measures included the HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression severity (CGI-S), and Beck Anxiety Inventory (BAI) for study outcomes, as well as C-SSRS, and Young Mania Rating Scale (YMRS) for assessment of adverse effects. Subjects were screened for serotonin syndrome utilizing the Hunter criteria[43] and for EMS[44,45] by clinician assessment at each visit. The Discontinuation Emergent Signs and Symptoms Checklist (DESS)[46] was administered

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during follow up visits at weeks 10 and 12 to monitor for symptoms related to discontinuation of the study medications. Safety labs (complete blood count, creatinine, blood urea nitrogen) were administered at the screening visit and at follow-up visits if indicated.

2.3 Statistical Analysis

Our primary outcome was change in HAM-D scores over 8 weeks of 5-HTP and creatine augmentation of subjects' baseline SSRI or SNRI. Change from mean HAM-D score from the screening and baseline visits over time was analyzed using repeated-measures linear mixed models.[47] HAM-D scores from the screening and baseline period were averaged and compared with the mean HAM-D scores from the treatment period, using last observation carried forward. MADRS and BAI scores were analyzed in a similar way. Each clinical score was considered the dependent variable in the linear mixed model. Week was included as a fixed factor and subject was treated as a random factor. Sidak correction was used to compensate for multiple comparisons, controlling for Type I error. Statistical significance was defined at an alpha level of corrected $p = 0.05$, two-tailed.

3. Results

3.1 Demographics and Baseline Symptoms

Fifteen women with a mean age of 34 ± 11.6 years were enrolled (Table 1). Twelve subjects completed the study. The subjects were moderately to severely ill at baseline, with a mean HAM-D score of 18.9 ± 2.5, a mean MADRS score of 25.4 ± 3.6, and a mean CGI-S score of 4.1 ± 0.3. Twelve patients were treated with an SSRI (fluoxetine, sertraline, escitalopram, citalopram, paroxetine), while 3 patients were treated with an SNRI (venlafaxine, duloxetine). All subjects had been taking at least the minimum recommended dose of their respective antidepressant according to the ATRQ for at least 8 weeks.

3.2 Effects of 5-HTP and creatine on depression and anxiety

Mean HAM-D scores improved significantly over the 8 weeks of treatment (18.9 ± 2.5 to 7.5 ± 4.4, $p < 0.00001$), representing an average 60.3% reduction from the baseline/screening visits (Table 2 and Figure 1). Ten patients (66.7%) met response criteria of at least a 50% reduction in HAM-D score. Seven patients (46.7%) met HAM-D remission criteria (HAM-D score ≤ 7).[48] There was no significant difference in HAM-D rating improvement with respect to baseline SSRI or SNRI use (60.4% vs 57.4%, $p = 0.88$).

Mean MADRS scores over 8 weeks were significantly reduced (25.4 ± 3.6 to 9.0 ± 6.6, $p < 0.00001$), representing an average 65% reduction (Figure 2). Twelve patients (80%) met MADRS response criteria (at least 50% reduction in MADRS score), and 8 patients (53%) met MADRS remission criteria (MADRS score < 10).[49] Improvements in anxiety were also significant, with BAI scores significantly reduced (22.7 ± 9.2 to 9.3 ± 6.4, $p < 0.00001$), representing a mean 59.9% decrease (Figure 3). CGI-S scores were also significantly improved (4.1 ± 0.4 to 1.9 ± 1.0, $p < 0.00001$)

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3.3 Safety and adverse events

Combination treatment with adjunctive 5-HTP and creatine was safe and well tolerated. Two participants withdrew from the study and were lost to follow-up. One subject described symptoms (increased anxiety, tremor) that raised concern for serotonin syndrome, but did not exhibit vital sign changes, physical exam abnormalities, or meet Hunter criteria for that condition. This subject was, however, withdrawn because of relapse of anorexia nervosa, which was deemed unrelated to study participation. A total of seven adverse events were recorded during the treatment period. These include cold/flu symptoms (n=1), kidney stones (n=1), urinary tract infection (n=1), diagnosis of medullary sponge kidney (n=1), injury/fall (n=2), night sweats/increased sweating (n=1). The only severe adverse event was the diagnosis of medullary sponge kidney disease, which was not attributed to study participation, as the condition is familial.[50] There was a trend toward mild weight gain during treatment (71.4 ± 19.3kg to 72.5 ± 19.8kg, p = 0.051), with the mean change being 1.1 ± 1.9kg. There were no significant changes in heart rate or blood pressure. There were no cases of serotonin syndrome, EMS, or treatment-emergent mania/hypomania based on YMRS scores. YMRS scores improved significantly from baseline by week 8 (1.2 ± 0.9 to 0.4 ± 1.1, p = 0.011). There was no treatment-emergent suicidal ideation based on C-SSRS, and there were no suicide attempts.

3.4 Discontinuation symptoms

Seven of the 12 study completers (58.3%) decided to continue treatment with creatine, 5-HTP, or both after the 8-week treatment period, though this required purchasing them over the counter. These subjects believed the treatment had been helpful and were reluctant to discontinue it. Accordingly, we were unable to collect adequate data regarding the effect of study drug cessation on discontinuation symptoms. There was no significant difference in DESS scores averaged over weeks 10 and 12 for subjects who elected to continue treatment versus those who did not (193.4 ± 13.2 vs 184.9 ± 10.3, p = 0.30).

4. Discussion

This study provides preliminary evidence that combination treatment with 5-HTP and creatine monohydrate may represent effective adjunctive treatment for women with MDD who have responded inadequately to SSRIs or SNRIs for at least 8 weeks. The treatment had few adverse effects, apart from a trend toward mild (~1kg) weight gain. Together, these factors suggest combination treatment with 5-HTP and creatine is a promising approach to antidepressant treatment and deserving of further study. The wide availability of both compounds is a further merit of the study, as it contributes to formalized understanding of the antidepressant effect of two nutritional supplements that are already in widespread use. Caution is still necessary, however, if only because of historical problems in guaranteeing the potency and safety of many nutritional supplements.

The study had obvious limitations. It is a small, open-label study without a placebo control. Likewise, combination treatment with 5-HTP and creatine makes it impossible to discern what proportion of patients' response was due to each medication, though comparison with historical controls treated with creatine or 5-HTP alone as augmentation might partially

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rectify this limitation. In Lyoo et al.,[29] subjects received escitalopram with adjunctive creatine or placebo. There, the change in mean HAM-D score at 8 weeks was 79.7%, while in the current study combining 5-HTP with creatine, it was only 60.3%. Nardini et al.[19] compared adjunctive 5-HTP 300mg daily or placebo in patients treated with clomipramine 50mg daily. At the end of four weeks, HAM-D scores had fallen by 57.7% in the 5-HTP group and by 40.7% in the placebo group, a significant difference. These studies would seem to indicate no synergistic benefit of combination treatment. But comparisons between response rates in the current and historical studies is limited by their intrinsic differences. In Lyoo et al., the mean reduction in HAM-D scores with placebo at 8 weeks was high, at 62.5%, subjects were more depressed at baseline (mean HAM-D score 26.9 vs 18.9), they had been free of psychotropic medication for ≥ 8 weeks, and 78.8% were antidepressant naïve. This is in stark contrast to the more treatment-resistant subjects studied here, all of whom were depressed despite ≥ 8 weeks of antidepressant monotherapy. In Nardini et al., the patients were hospitalized, were somewhat more ill at baseline, were treated for only four weeks, and were started on 5-HTP or placebo at the same time as clomipramine. Accordingly, historical controls do not exclude the possibility of synergistic benefit.

Another limitation is that, although the subjects were persistently depressed, with an average symptom duration of 395.2 ± 286.0 weeks, we did not obtain complete medication histories to ascertain whether they met standard criteria for treatment-resistance (failure of at least 2 antidepressant trials). Additionally, baseline antidepressant doses for some subjects were in the low therapeutic range, and participants were taking a variety of antidepressants, creating sample heterogeneity. The study also focused on adult women, limiting its generalizability.

Finally, these data were collected at the moderately high altitude of Salt Lake City, Utah, so that our efficacy, tolerability and safety results may not generalize to women residing at altitudes nearer sea level. This is because alterations in serotonin metabolism and brain bioenergetics have been linked to hypoxia, and increased altitude of residence can produce chronic hypobaric hypoxia (reduced blood oxygen because of reduced atmospheric pressure).[51,52] Hypoxia may reduce the efficiency of serotonin synthesis, as the activity of tryptophan hydroxylase is oxygen-dependent, and the conversion of tryptophan to 5-HTP by tryptophan hydroxylase is the rate-limiting step in serotonin production.[53] Indeed, simulated high altitude decreases levels of serotonin[54] and reduces response to fluoxetine[55] in rodent models. Altitude and hypobaric hypoxia can also affect brain bioenergetics. Healthy individuals residing at 1370m (Salt Lake City, UT) show reduced inorganic phosphate levels and increased brain pH compared to those residing near sea level (Belmont, MA or Charleston, SC).[56] In rodents, hypobaric hypoxia increases the ratios of cellular metabolites like inositol to total creatine in the frontal cortex,[57] which is compatible with reductions in total creatine level. Accordingly, the women participating in this study may have been more likely than women residing at sea level to respond to the intervention, and, because of reduced basal serotonin synthesis, less likely to develop serotonin syndrome.

This small, open-label study of combined 5-HTP and creatine monohydrate as adjunctive treatment for major depressive disorder in women not responsive to an SSRI or SNRI demonstrated robust symptomatic improvement and good safety and tolerability, although its short duration of 12 weeks prevents us from reaching conclusions about the interventions'

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long term adverse effects. Further research on this treatment is merited, including definitive randomized placebo-controlled trials, trials including men, multi-arm trials comparing 5-HTP to creatine to the combination, and trials involving the incorporation of biomarkers of treatment response, including neuroimaging modalities and measurements of serotonin synthesis.

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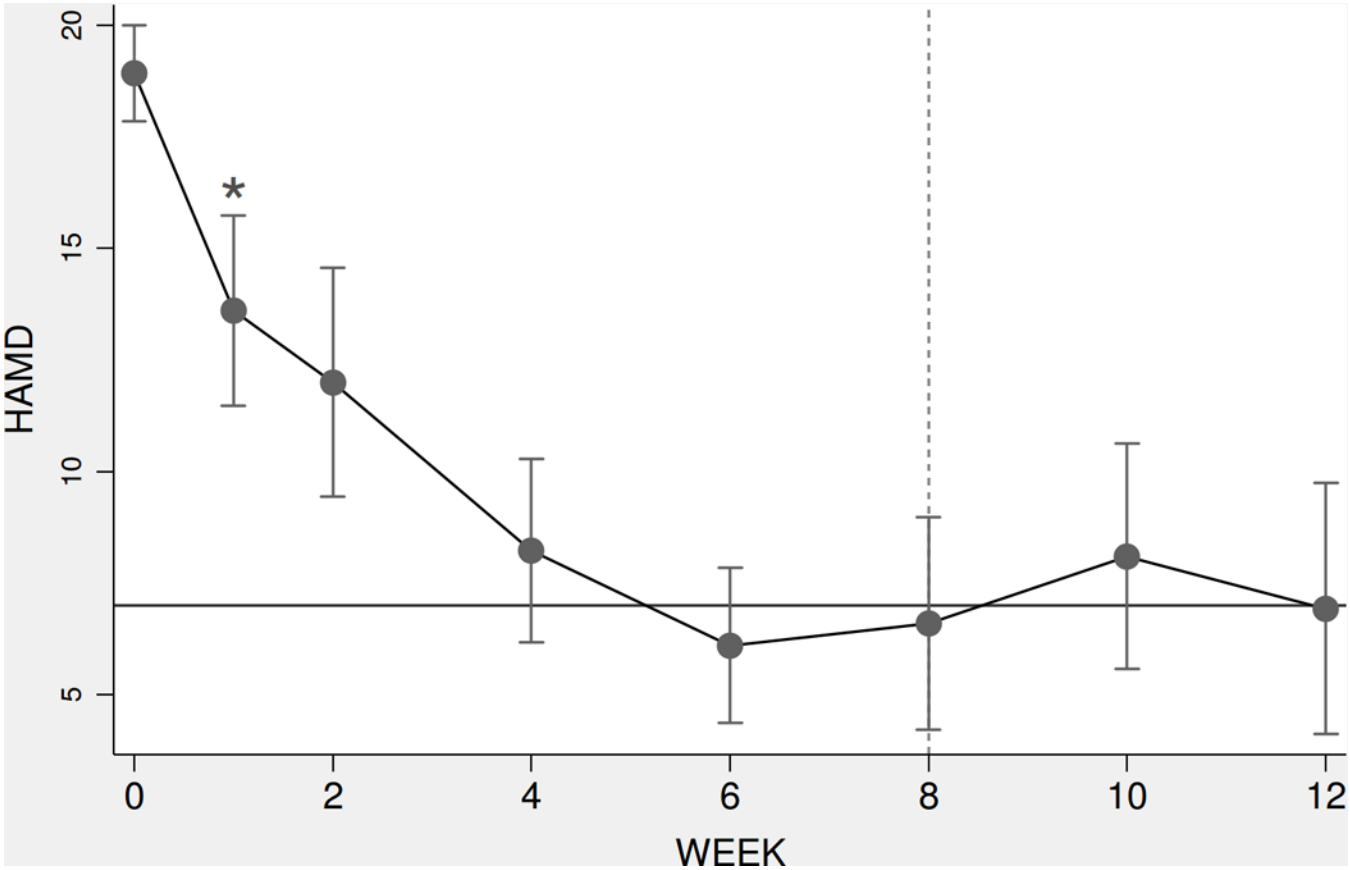

Figure 1.

HAM-D scores over 8 weeks in women receiving SSRI/SNRI augmentation with 5-HTP and creatine. Active treatment provided through week 8; weeks 10 and 12 represent post-treatment follow-up. Error bars represent 95% confidence interval of the mean. Solid horizontal line indicates potential remission score (HAM-D=7). Asterisk (*) represents beginning of statistical significance compared to baseline (Sidak corrected $p < 0.05$). Dashed vertical line indicates the finish of 8 weeks of treatments.

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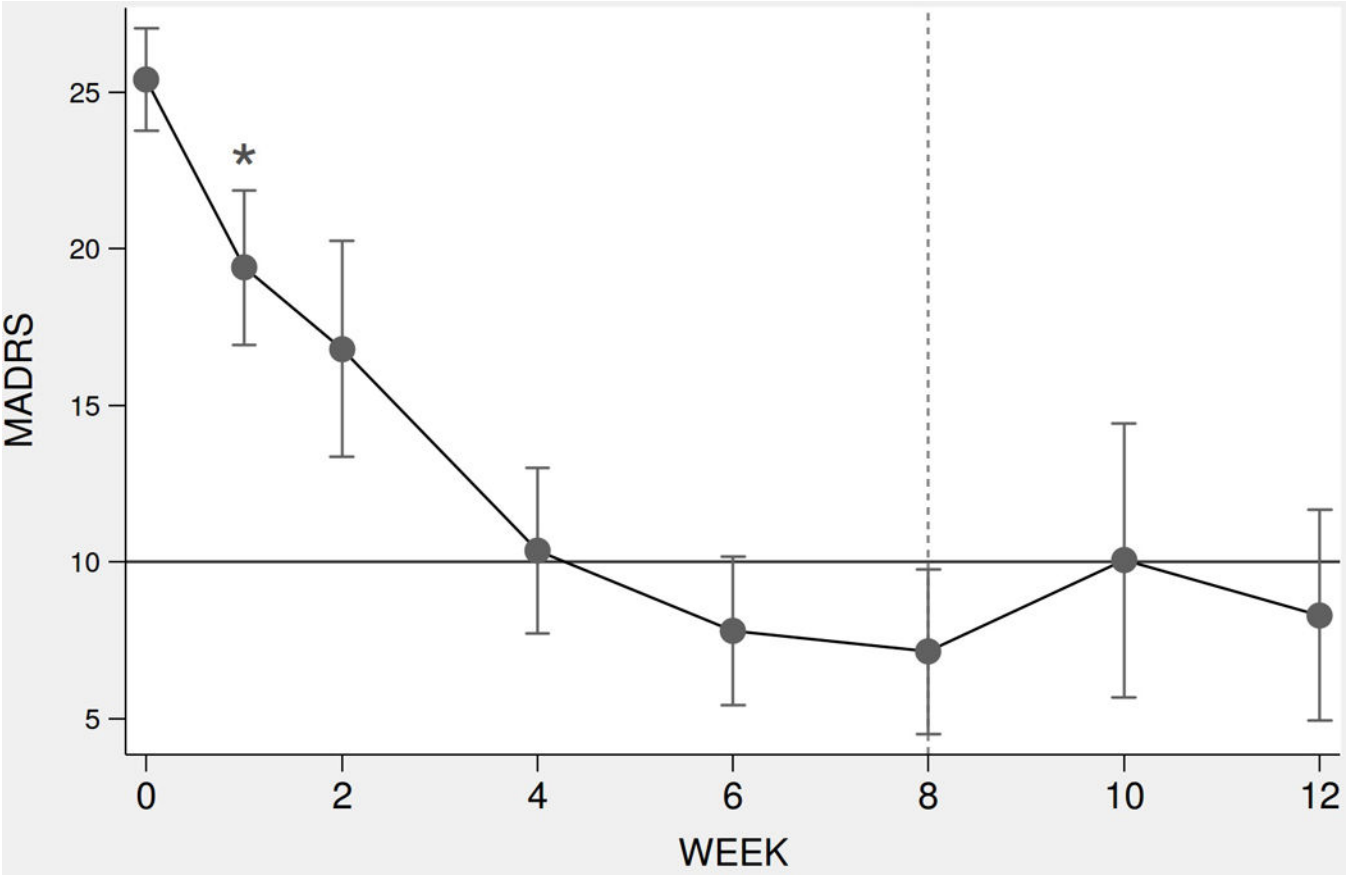

Figure 2.

MADRS scores over 8 weeks in women receiving SSRI/SNRI augmentation with 5-HTP and creatine. Active treatment provided through week 8; weeks 10 and 12 represent post-treatment follow-up. Error bars represent 95% confidence interval of the mean. Solid horizontal line indicates potential remission score (MADRS=10). Asterisk (*) represents beginning of statistical significance compared to baseline (Sidak corrected $p < 0.05$). Dashed vertical line indicates the finish of 8 weeks of treatments.

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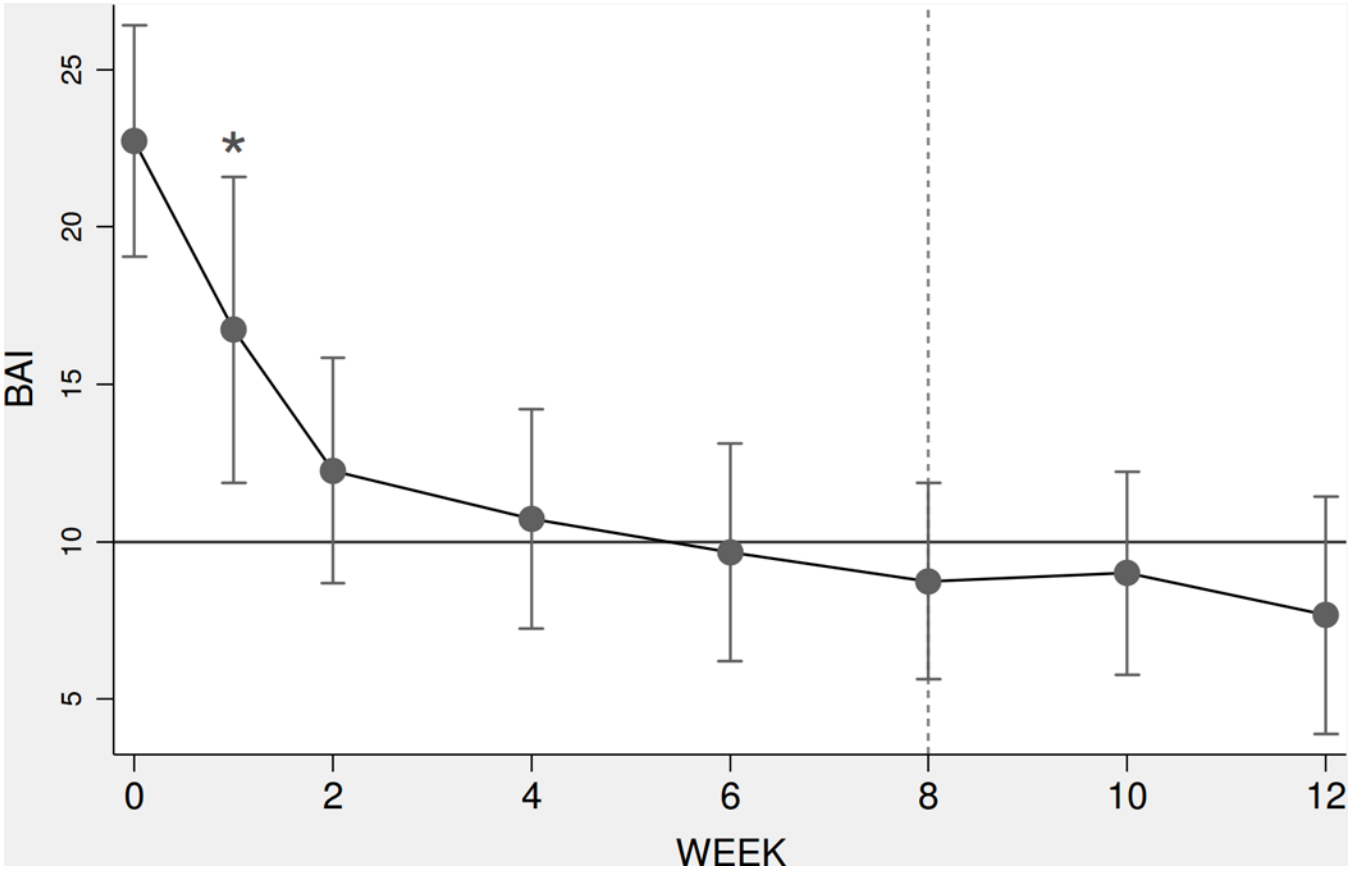

Figure 3.

BAI scores over 8 weeks in women receiving SSRI/SNRI augmentation with 5-HTP and creatine. Active treatment provided through week 8; weeks 10 and 12 represent post-treatment follow-up. Error bars represent 95% confidence interval of the mean. Solid horizontal line indicates potential remission score (BAI=10). Asterisk (*) represents beginning of statistical significance compared to baseline (Sidak corrected $p < 0.05$). Dashed vertical line indicates the finish of 8 weeks of treatments.

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Table 1

Baseline characteristics of women receiving SSRI/SNRI augmentation with 5-HTP and creatine

Characteristic		Value
N		15
Age (years)		34 ± 11.6
Race		
	Caucasian	15 (100%)
	Other	0 (0%)
Mean Weeks Ill		395.2 ± 286.0
Antidepressant Types and Doses		N (mean dose)
SSRIs	Escitalopram	3 (16.7mg)
	Citalopram	2 (35mg)
	Fluoxetine	2 (40mg)
	Paroxetine	1 (20mg)
	Sertraline	4 (62.5mg)
SNRIs	Duloxetine	1 (40mg)
	Venlafaxine	2 (150mg)

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Table 2

Efficacy and safety data for women receiving SSRI/SNRI augmentation with 5-HTP and creatine

Outcomes Measure	Pretreatment Mean ± SD	Week 8 Mean ± SD
HAM-D	18.9 ± 2.5	7.5 ± 4.4, $p < 0.00001$
MADRS	25.4 ± 3.6	9.0 ± 6.6, $p < 0.00001$
BAI	22.7 ± 9.2	9.3 ± 6.4, $p < 0.00001$
CGI	4.1 ± 0.4	1.9 ± 1.0, $p < 0.00001$
YMRS	1.2 ± 0.9	0.4 ± 1.1, $p = 0.011$
Weight	71.4 ± 19.3kg	72.5 ± 19.8kg, $p = 0.051$