European Neuropsychopharmacology 90 (2025) 28–35

Contents lists available at ScienceDirect

European Neuropsychopharmacology

journal homepage: www.sciencedirect.com/journal/european-neuropsychopharmacology

# Efficacy and safety profile of oral creatine monohydrate in add-on to cognitive-behavioural therapy in depression: An 8-week pilot, double-blind, randomised, placebo-controlled feasibility and exploratory trial in an under-resourced area

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ARTICLE INFO

*Keywords:*
Depression
Creatine
Cognitive-behavioural therapy
Nutraceutical
Clinical trial

ABSTRACT

Pre-clinical and clinical evidence proposes that creatine monohydrate, an affordable nutraceutical, could be a useful adjunct to conventional antidepressant treatments. In this pilot feasibility and exploratory study, we investigate the 8-week effects of creatine in addition to cognitive-behavioural therapy (CBT) versus placebo plus CBT in depression. For the primary efficacy outcome of change in Patient Health Questionnaire-9 depression score at study endpoint, we used mixed-model repeated measures analysis of covariance. Logistic regressions were employed to assess acceptability (any-cause dropouts), tolerability (dropouts for adverse events), and safety (patients experiencing one or more adverse events). We calculated effect sizes adjusted for age, sex, and baseline depression score. One-hundred participants (50 females, mean age= 30.4 ± 7.4 years) with depression (mean PHQ-9 = 17.6 ± 6.3) were randomised to either creatine+CBT ($N = 50$) or placebo+CBT ($N = 50$). At 8 weeks, PHQ-9 scores were lower in both study arms, but significantly more so in participants taking creatine (mean difference= -5.12). Treatment discontinuations due to any cause and to adverse events, and proportion of participants with at least one adverse event were comparable between study arms. This hypothesis-generating trial suggests that creatine could be a useful and safe supplement to CBT for depression. Longer and larger clinical trials are warranted.

## 1. Introduction

Major depressive disorder has a large prevalence (> 350 million people worldwide) and burden of disease (GBD 2019 Mental Disorders Collaborators, 2022). It is diagnosed when an individual has a persistently low or depressed mood, anhedonia or decreased interest in pleasurable activities, feelings of guilt or worthlessness, lack of energy, poor concentration, appetite changes, psychomotor retardation or agitation, sleep disturbances, or suicidal thoughts (Bains and Abdijadid, 2023). Psychotherapy and pharmacotherapy are both (Cuijpers et al., 2021a; Furukawa et al., 2021) and similarly (relative risk = 0.99, 95 % confidence interval = 0.92 to 1.08) (Cuijpers et al., 2020) efficacious in treating depressive disorders. Nevertheless, between one-third and one-quarter of patients do not respond to any antidepressant strategy (Rush et al., 2019) or drop out from any treatment due to inefficacy or adverse events (Cipriani et al., 2018; Ghaemian et al., 2020), such as insomnia, anxiety, fatigue, sexual dysfunction, and weight gain (Chevance et al., 2022). Hence, novel augmentation techniques that are

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https://doi.org/10.1016/j.euroneuro.2024.10.004
Received 4 June 2024; Received in revised form 6 October 2024; Accepted 14 October 2024
Available online 1 November 2024

accessible, affordable, and capable of increasing treatment efficacy can be useful adjuncts to evidence-based treatments for depression.

Creatine monohydrate (creatine) is a safe and inexpensive nutraceutical (i.e., a subset of food such as dietary supplements) that can reach the central nervous system (Lyoo et al., 2003). Aside from being naturally present in food (milk, meat, fish), endogenous creatine is synthesised in the liver and in the brain, where it is normally stored in high concentrations and serves important functions for its energy metabolism (Wyss and Kaddurah-Daouk, 2000). Altered regulation of brain energy stores, especially in the form of low creatine levels (Faulkner et al., 2021), has been associated with both depressive symptoms and resistance to pharmacological or behavioural treatments in animals and humans (Kious et al., 2019; Pazini et al., 2019). Furthermore, creatine is a neuroprotective (anti-apoptotic, anti-oxidative, anti-nitrosative) agent, and modulates neuroreceptors (serotonin, noradrenaline, dopamine, adenosine, N-methyl-d-aspartate [NMDA]) implicated in depression while also interacting with established antidepressant medications (Kious et al., 2019; Pazini et al., 2019). On these mechanistic bases, it has been hypothesised that the pleiotropic activities of creatine supplementation may contribute to a greater response to conventional antidepressant strategies. Numerous reviews have summarised data from pre-clinical and clinical studies that support its use for improving the treatment of depressive disorders (Candow et al., 2023; Forbes et al., 2022; Kious et al., 2019; Pazini et al., 2019; Roschel et al., 2021; Sarris et al., 2016). Creatine reliably produces antidepressant-like effects in animal models of depression, particularly in female specimens (Allen et al., 2010, 2012, 2015; Kanekar et al., 2021). Likewise, preliminary evidence from several clinical trials suggests that creatine, given in addition to conventional antidepressant medications, can reduce depressive scores with moderate to large effect sizes while possibly improving cognition in patients with unipolar or bipolar depression (Kious et al., 2017; Kondo et al., 2011, 2016; Lyoo et al., 2012; Roitman et al., 2007; Toniolo et al., 2017, 2018). Most of these trials, however, did not include a placebo arm (Kious et al., 2017; Kondo et al., 2011, 2016; Roitman et al., 2007). The largest randomised controlled trial (RCT) to date used creatine in add-on to selective-serotonin reuptake inhibitors (SSRI); it only included 52 participants, who were exclusively women, and showed a reduction in depression scores as well as comparable dropouts and reported adverse events over two months (Lyoo et al., 2012). Two further RCTs in patients with bipolar depression suggested a possible effect of creatine on cognitive measures and remission rates (Toniolo et al., 2017, 2018), though two instances of switch to hypomania/mania were identified in the creatine group (Toniolo et al., 2018). amongst several approaches to treat depression, cognitive-behavioural therapy (CBT) consistently shows positive outcomes across different formats, patient groups, and settings, but slow and unsatisfactory response rates remain an issue (Cuijpers et al., 2023). In this context, creatine could enhance the effects of CBT by promoting cognitive and behavioural functioning while also expressing a direct antidepressant action – but to present this has not been tested in a clinical trial setting. Thus, in this proof-of-concept study, we investigate the 8-week augmentative antidepressant efficacy, acceptability, tolerability, and safety of creatine by combining oral creatine monohydrate with CBT against placebo with CBT in a community sample of patients diagnosed with depression. Based on prior studies (Kious et al., 2017; Kondo et al., 2011, 2016; Lyoo et al., 2012; Roitman et al., 2007; Toniolo et al., 2017, 2018), we hypothesised that people on creatine and CBT would show lower depression scores as well as similar treatment discontinuations and adverse events to those on CBT alone after 8 weeks.

## 2. Methods

This study is a pilot (phase 2, nutraceuticals), randomised, parallel-arm, placebo-controlled, double-blind, feasibility and exploratory trial, approved and funded by the Universal Human Rights and Social Development Association (UHRSDA) Institutional Ethics Committee on the 10th of November 2020, reference ECR/4263/MH/UK/2020/RR-21 (https://www.uhrsda.com/post/institutional-ethics-committee-uhrsda-certificate-for-mr-nima-norbu-sherpa, Supplementary Material, S1).

### 2.1. Participants

Potential participants were approached via survey method (i.e., research staff installed a stall during the study period) at three sites (Chandrabani, outside Graphic Era Hill University, MDDA Park) in Dehradun, India. The recruitment centre was run by UHRSDA, a government-registered charity organisation. As the trial run between 2020–2021, precautions to avoid the spread of Covid-19 infections were taken according to governmental guidance (Raman et al., 2021); however, infections were not tracked during the study. Screening was performed by trained members of the research team (clinical psychologist SD, senior research nurse TD) using a semi-structured interview form according to the following inclusion criteria to determine eligibility: a) an age between 18 and 60 years; b) a board-registered clinical psychologist diagnosis of major depressive disorder/recurrent depressive disorder with a current depressive episode as defined by the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5 (SCID-5) (First et al., 2016); c) a score $\geq$5 on the Patient Health Questionnaire (PHQ)−9, therefore ranging from mild (5–9), moderate (10–14), moderate-severe (15–19), and severe ($\geq$20) depression (Kroenke et al., 2001); d) no clinically significant physical or mental disorder other than depression (patients with depression in the context of a bipolar disorder or patients with psychotic depression were excluded); e) no history of alcohol or substance misuse; f) no use of any psychotropic drugs (e.g., benzodiazepines, antidepressants, mood stabilisers/anticonvulsants, antipsychotics) for at least eight weeks before the screening evaluation; g) no known allergy or intolerance to creatine or starch; h) acceptance to use an appropriate contraceptive method, including abstinence, during participation in the study and throughout the evaluation period; i) no pregnant or breast-feeding woman; j) ability to understand and willingness to sign an approved written informed consent document.

### 2.2. Intervention and comparator

enroled participants were randomised to receive one of two treatments: 5 g/day of oral creatine monohydrate – a dose successfully used in previous trials on depression (Kious et al., 2019; Pazini et al., 2019) along with biweekly individual CBT (creatine + CBT arm) or 5 g/day of oral starch along with biweekly individual CBT (placebo + CBT arm). Oral creatine monohydrate and starch capsules (placebo) were identical in terms of appearance, odour, taste, and packaging. The common comparator (i.e., individual CBT) was delivered with low frequency (biweekly) to cater for the setting's limited resources, over five (at week 0, 2, 4, 6, and 8) 45-minute session by a board-registered clinical psychologist (SD). This low-intensity intervention (Bennet-Levy et al., 2010) follows principles of Beck's CBT with a focus on psychoeducation, cognitive restructuring, and behavioural activation/modification, and includes in-between-session homework such as thought logbooks and activity charts. Protocol fidelity was audited by an external consultant clinical psychologist after trial completion, by randomly selecting a participant from each arm of the trial – further details provided in Supplementary Material, S2.

### 2.3. Outcomes

The primary outcome was the depressive symptom severity (efficacy), measured with the PHQ-9 (Kroenke et al., 2001) at study endpoint i.e., 8 weeks – a common timepoint for trials in depression (Cipriani et al., 2018; Cuijpers et al., 2020). Secondary outcomes were the proportion of patients discontinuing treatment due to any cause

(acceptability), the proportion of patients discontinuing treatment due to adverse events (tolerability), and the proportion of patients experiencing at least one adverse event (safety) reported on a pre-specified Side Effect Questionnaire (SEQ, Supplementary Material, S3) at study endpoint – as per several clinical trials (Cipriani et al. 2018; Kishi et al., 2023). The type, severity, and total number of reported adverse events were also recorded.

### 2.4. Study procedures

Eligible participants were provided with a participant information sheet and given enough time to read it and ask any questions about the study-related procedures, and their informed consent was received. Because of the higher prevalence of depression in women, recruiting staff was advised to stop further recruitment of the latter once the target number of participants was reached (see sample size calculation below). Trained research staff (clinical psychologist SD, senior research nurse TD) collected relevant socio-demographic data (age, sex assigned at birth, relationship status, education in years, employment status) and obtained medical and psychiatric histories using a semi-structured interview form, performed a general physical examination (e.g., measurement of blood pressure and body mass index [BMI], check for marks of intravenous drug use), and administered the PHQ-9 as part of the screening phase. enroled participants were randomised (1:1, stratified by age and sex assigned at birth) according to a software code designed by an external investigator not otherwise involved in the study; key linking codes were recorded on a registry kept in a dual custody vault (Supplementary Material, S4) during the entire trial period. Randomised participants were provided instructions on how to take the study drug/placebo every day at any preferred time of the day (i.e., whether in the morning or in the evening), with or without food. Compliance was supported via daily reminders (i.e., automated text or phone call by research staff, according to preference) as well as a calendar app reminder on their phone set up on the day of enrolment. Follow-up visits were scheduled at week 2, 4, 6, and 8 (± 24 h) from the day of randomisation. On each research visit, participants were reminded of the study procedures and completed the PHQ-9 and SEQ questionnaires; then, they received a 45-minute CBT session. No other psychotropic drug use or psychotherapy were permitted until after the end of the trial. Participants who withdrew their consent, were lost to follow-up, or breached study protocol were not replaced.

### 2.5. Sample size calculation

To our knowledge, no prior trial had investigated the use of creatine in addition to a psychological intervention for depression. Based on a previous clinical trial comparing creatine + SSRI (mean depression score at endpoint = 5.4, standard deviation = 3.0) vs placebo + SSRI (mean depression score at endpoint = 9.8, standard deviation = 3.5) (Lyoo et al., 2012), using the *pwr* R package, we calculated that 30 participants would provide 95 % power with $\alpha = 0.05$ to detect changes of a comparable magnitude on our primary efficacy measure. However, to account for the significant differences in the intervention/comparator under investigation (creatine + CBT vs placebo + CBT) and the expected elevated number of dropouts due to the Covid-19 pandemic during the conduction of the trial, we sought to recruit 50 participants per study arm.

### 2.6. Statistical analysis

Data analysis was conducted on an intention-to-treat (ITT, i.e., any eligible participant randomised, according to their study arm) approach. To handle missing outcome data (missing at random assumption), we generated 10 multiply imputed datasets using a Bayesian mixed model repeated measures (MMRM) with non-informative priors, and combined them according to the Rubin's rules using the *brms* and *mice* R packages (Bürkner et al., 2017; van Buuren and Groothuis-Oudshoornm 2011). For the primary outcome of difference in depression scores at study endpoint (i.e., week 8), we performed an analysis of covariance (ANCOVA) model with study arm as an independent factor, and age, sex assigned at birth, and baseline depression score as covariates, as per previous trials (Lyoo et al., 2012). We also conducted a per-protocol analysis (PP, i.e., including completers-only and no imputed data at the 8-week study endpoint, according to their study arm) as a sensitivity analysis. For the secondary outcomes of acceptability, tolerability, and safety at study endpoint, we performed a logistic regression with study arm as an independent factor, and age, sex assigned at birth, and baseline depression score as covariates, as above. We computed adjusted mean differences (aMD, for continuous variables) or odds ratio (aOR, for dichotomous variables) with 95 % confidence intervals (95 %CI) for all outcomes measures at study endpoint.

All the analyses were performed using R 4.3.1 (Beagle Scouts) or SPSS 29.0 (StataCorp, 2023; R Core Team, 2023).

## 3. Results

A total of 156 people were assessed for eligibility: 100 participants were randomised to either the creatine + CBT arm or the placebo + CBT arm. Of these, 60 participants reached the study endpoint at 8 weeks (Fig. 1). All randomised participants were accounted for in the intention-to-treat analyses.

### 3.1. Baseline characteristics

Participants' baseline characteristics were comparable between study arms (Table 1). Across the sample of 100 participants (50 females), the mean age was 30.4 years (±7.4) and mean BMI 26.9 (±3.0). Mean PHQ-9 score was 17.6 (±6.3), consistent with moderately-severe depression; scores ranged from mild (= 5 for creatine + CBT arm, = 6 for placebo + CBT arm) to severe (= 27 for both creatine + CBT and placebo + CBT arms) (Kroenke et al., 2001).

### 3.2. Study outcomes

Additional details on depression symptom severity scores, treatment discontinuations (due to any cause and due to adverse events), and adverse events (number of patients experiencing at least one, total number, number by type) at each timepoint are provided in Supplementary Material, S5. Outcome data at study endpoint for both creatine + CBT and placebo + CBT arms are available in Table 2.

PHQ-9 scores at study endpoint were lower than baseline ones for both arms: 5.8 (±4.8) for creatine + CBT arm (i.e., mild depression) and 11.9 (±6.6) for placebo + CBT arm (i.e., moderate depression), with twelve and five participants respectively achieving remission (i.e., PHQ-9 score less than 5) (Kroenke et al., 2001). For the primary efficacy outcome of difference in depression symptoms severity scores measured on the PHQ-9 at 8 weeks, ITT analysis showed that patients randomised to the creatine + CBT arm were associated with lower depression symptom severity scores compared to those randomised to the placebo + CBT arm (aMD = −5.12, 95 %CI = −7.20 to −3.52, favouring the creatine + CBT arm). Higher baseline depressive symptom severity scores were associated with a smaller post-treatment reduction. The PP sensitivity analysis (i.e., excluding imputed data) showed analogous results, namely study completers at 8 weeks randomised to the creatine + CBT arm had lower depression symptom severity scores compared to those randomised to the placebo + CBT arm ($N = 30$ per study arm, aMD = −6.07, 95 %CI = −7.88 to −4.25, favouring the creatine + CBT arm).

The proportion of participants discontinuing treatment due to any cause at study endpoint were high for both study arms (20 per arm) (aOR = 0.96, 95 %CI = 0.31 to 2.22); of these, nine and eight were due to adverse events in the creatine + CBT arm and in the placebo + CBT arm, respectively (aOR = 0.81, 95 %CI = 0.27 to 2.42).

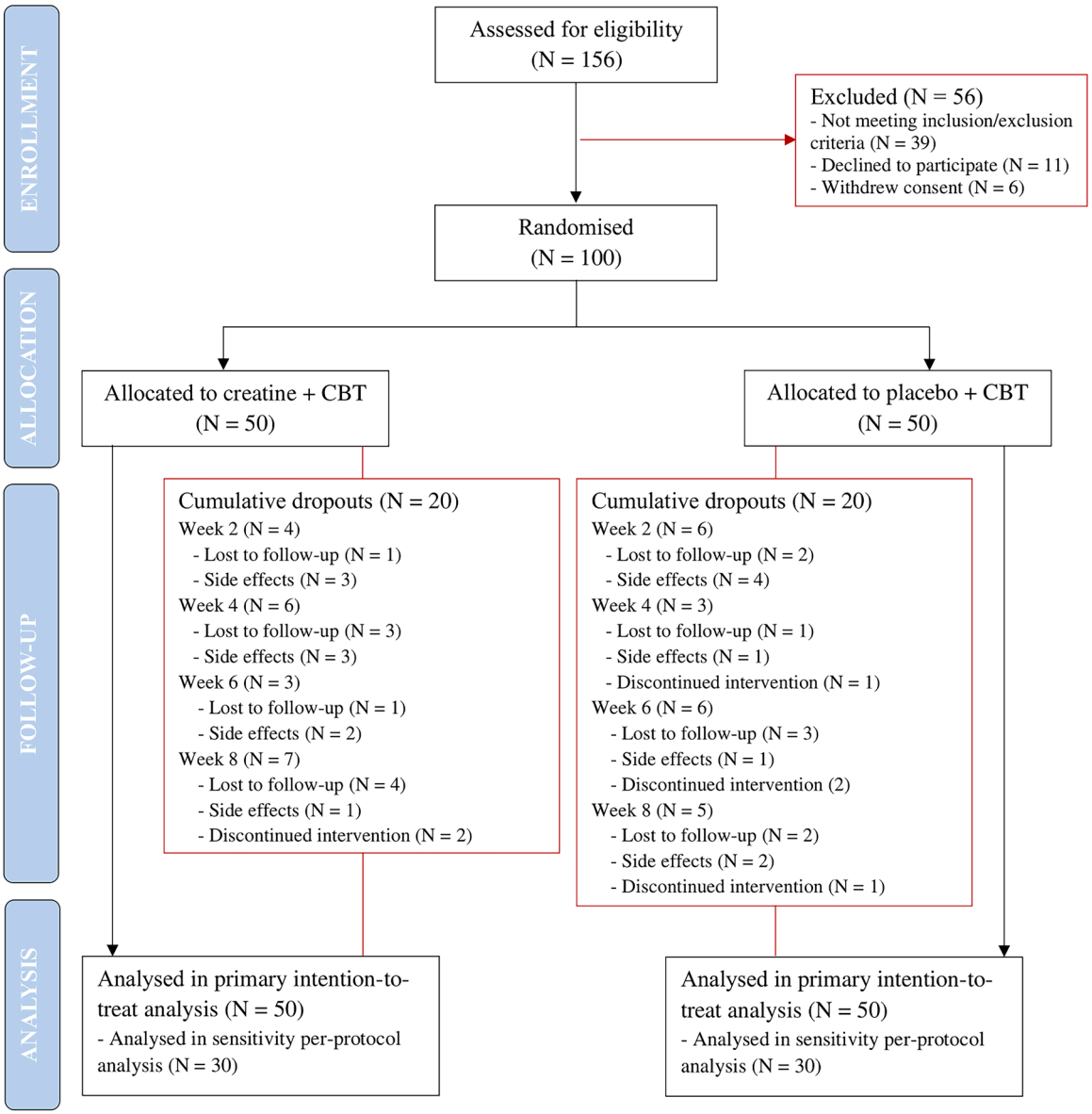


**Fig. 1.** Study flow chart.

**Table 1**
Baseline characteristics per study arm.

| *Characteristic* | Creatine + CBT *N* = 50 | Placebo + CBT *N* = 50 |
|---|---|---|
| Age | 30.5 (±7.0) | 30.3 (±7.8) |
| Sex | | |
| Male | 25 (50 %) | 25 (50 %) |
| BMI | 27.3 (±2.6) | 26.6 (±3.4) |
| Relationship status | | |
| Single | 31 (62 %) | 30 (60 %) |
| Married | 16 (32 %) | 17 (34 %) |
| Separated | 2 (4 %) | 2 (4 %) |
| Divorced | 1 (2 %) | 1 (2 %) |
| Education in years | 15.8 (±1.5) | 15.5 (±1.7) |
| Employment status | | |
| Employed | 26 (52 %) | 25 (50 %) |
| Unemployed | 22 (44 %) | 23 (46 %) |
| On sick leave | 2 (4 %) | 2 (4 %) |
| PHQ-9 baseline | 17.8 (±6.1) | 17.6 (±6.4) |

Legend. Values are means (standard deviations) or numbers (percentages). BMI: body mass index; PHQ-9: Patient Health Questionnaire-9.

By study completion, 30 participants randomised to the creatine + CBT arm experienced at least one adverse event compared to 34 in the placebo + CBT arm: overall, safety of treatment was comparable (aOR = 1.83, 95 %CI = 0.77 to 4.35). A total of 127 adverse events were reported on the SEQ: 69 in the creatine + CBT arm and 58 in the placebo + CBT arm. Gastrointestinal adverse event, especially altered bowel habits, were the most reported in both the creatine + CBT and placebo + CBT arms: respectively, 14 and 11 reports of constipation, 15 and 6 of diarrhoea. Next, there were 12 reports of muscle cramps in the creatine + CBT arm and 7 in the placebo + CBT arm. The frequency of most adverse events was similar between study arms; however, diarrhoea (15 vs 6 reports) and abdominal pain (9 vs 1 reports) were more frequently reported in the creatine + CBT arm, while vomiting (2 vs 9 reports) and pruritus (4 vs 11 reports) were more common in the placebo + CBT arm. Adverse events were reported more often at the beginning of treatment (49 reports over weeks 2 to 4) for the creatine + CBT arm, while they were similarly distributed across the 8 weeks of treatment in the placebo + CBT arm. The severity of adverse events was generally mild ($N = 27$ for creatine + CBT arm and $N = 30$ for placebo + CBT arm scored them = 1 on the SEQ), and no serious ones were recorded. One patient

**Table 2**
Study outcomes at 8 weeks (study endpoint).

| | **Creatine + CBT** N = 50 | **Placebo + CBT** N = 50 | ***Intention-to-treat analysis*** *Adjusted model* N = 100 (50 per study arm) | | |
|---|---|---|---|---|---|
| | *Mean (±SD)* | *Mean (±SD)* | *Variable* | *aMD/β* | *95% CI* |
| **PHQ-9 depression symptom severity at endpoint (efficacy)** | *Baseline:* 17.8 (±6.1) | *Baseline:* 17.6 (±6.4) | Study arm | **-5.12** | **-7.20, -3.52** |
| | | | Age | 0.05 | -0.05, 0.15 |
| | 5.8 (±4.8) | 11.9 (±6.6) | Sex | -0.48 | -2.31, 1.34 |
| | | | Baseline PHQ-9 | **0.79** | **0.66, 0.93** |
| | *N events (%)* | *N events (%)* | *Variable* | *aOR/β* | *95% CI* |
| **Proportion of participants discontinuing treatment due to any cause (acceptability)** | 20 (40.0%) | 20 (40.0%) | Study arm | 0.96 | 0.31, 2.22 |
| | | | Age | 0.96 | 0.90, 1.02 |
| | | | Sex | 1.00 | 0.43, 2.31 |
| | | | Baseline PHQ-9 | **0.91** | **0.85, 0.98** |
| **Proportion of participants discontinuing treatment due to adverse events (tolerability)** | 9 (18.0%) | 8 (16.0%) | Study arm | 0.81 | 0.27, 2.42 |
| | | | Age | 0.92 | 0.83, 1.01 |
| | | | Sex | 2.18 | 0.72, 6.67 |
| | | | Baseline PHQ-9 | 0.94 | 0.87, 1.03 |
| **Proportion of participants with at least one adverse event (safety)** | 30 (60.0%) | 34 (68.0%) | Study arm | 1.83 | 0.77, 4.35 |
| | | | Age | **1.08** | **1.01, 1.16** |
| | | | Sex | 0.99 | 0.42, 2.23 |
| | | | Baseline PHQ-9 | 1.05 | 0.98, 1.12 |

***Legend.*** Figures in **bold** are statistically significant ($p < 0.05$). Efficacy < 0 favours creatine + CBT; acceptability, tolerability, safety > 1 favours creatine + CBT. aMD: adjusted mean difference; aOR: adjusted odds ratio; β: beta coefficient; CBT: cognitive behavioural therapy; CI: Confidence Interval; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation.

experienced significant diarrhoea (SEQ score = 4) in the creatine + CBT arm. No episodes of self-harm or suicidal ideation, or manic switches were observed.

## 4. Discussion

This pilot, double-blind, randomised, placebo-controlled feasibility and exploratory trial over 100 community patients with a diagnosis of depression showed that 8-week treatment with oral creatine monohydrate with CBT compared to placebo with CBT, was similarly acceptable, tolerable, and safe, and associated with a greater decrease of depressive symptoms compared to placebo-augmented CBT.

Over the course of 8 weeks of treatment, both study arms displayed a meaningful reduction of PHQ-9 depression scores, which is comparable to the effects seen in several clinical trials of CBT (Cuijpers et al., 2023). Nonetheless, depression scores were significantly lower when CBT was augmented with 5 mg of creatine monohydrate (both in the primary ITT analysis and in the sensitivity PP analysis), in line with the results of previous clinical trials of creatine in addition to antidepressant medications (Kious et al., 2017; Kondo et al., 2011, 2016; Lyoo et al., 2012; Roitman et al., 2007; Toniolo et al., 2018). To date (Kious et al., 2019; Pazini et al., 2019), only one small ($N = 18$) randomised controlled trial (RCT) on patients with treatment-resistant depression did not observe any positive effect of a short course (2-week) of creatine 5–10 mg administration in addition to one of several antidepressants compared to an antidepressant medication alone (Nemets and Levine, 2013). Conversely, the largest ($N = 52$ women with major depressive disorder) RCT thus far found a large effect size (Cohen's $d = 1.13$, 95 %CI = 0.75 to 1.52) on the Hamilton Depression Rating Scale (HAM-D) when comparing the effect of creatine 3–5 mg in addition to the antidepressant escitalopram against escitalopram plus placebo at 8 weeks (Lyoo et al., 2012). Compared to this study, our trial showed a similarly large effect size, while also including a higher number of participants of both sexes, which increases the generalisability of its results. In fact, differently from several pre-clinical (Allen et al., 2010, 2012, 2015; Kanekar et al., 2021) and clinical studies (Kious et al., 2017; Kondo et al., 2011, 2016; Lyoo et al., 2012), sex did not appear to modify the efficacy of the creatine augmentation in our trial – which can be informative to further adequately powered RCTs.

Unlike all prior trials that had investigated creatine as an adjunct to antidepressant medications (Kious et al., 2017; Kondo et al., 2011, 2016; Lyoo et al., 2012; Roitman et al., 2007; Toniolo et al., 2017, 2018), we used a psychological intervention, namely CBT, as the common comparator. The mechanistic bases for the putative augmenting effect of creatine on antidepressant drugs have been investigated in pre-clinical studies, which have highlighted interactions with monoamine systems [serotoninergic (Cunha et al., 2013) and dopaminergic (Cunha et al., 2012)] implicated in depression and with antidepressants that act on them. From this perspective, our finding that creatine could augment the effect of CBT is novel and its mechanistic basis unknown. An earlier RCT had shown that creatine could improve cognitive measures in patients with unipolar and bipolar depression (Toniolo et al., 2017). Low levels of creatine in the prefrontal cortex have been associated with depressive symptomatology (Faulkner et al., 2021), thus restoring prefrontal creatine and related metabolites (Yoon et al., 2016) could be of importance for effective psychotherapy because this brain area is implicated in CBT functioning (Yuan et al., 2022). Whether similar benefits could be observed for other psychological treatments requires further research. It is possible that creatine could express a direct antidepressant activity, as advised by some experimental data (Hellem et al., 2015), or a protective effect by reducing the risk of depression, as seen in a recent observational study (Bakian et al., 2020). These latter findings, if further validated, might have implications for public health – though clinical trials of creatine in healthy volunteers have failed to show any cognitive or emotional effect (Alves et al., 2013), while the role of creatine-rich or -poor diets onto brain health remains ambiguous (Kious et al., 2019).

In our sample, treatment discontinuations were common (40 %) – an issue that is well-known in patients with depressive illness (Cipriani et al., 2018; Ghaemian et al., 2020). Our figures are slightly higher than those of other comparable RCTs (20 % to 38 %) (Kious et al., 2017; Lyoo et al., 2012; Roitman et al., 2007; Toniolo et al., 2018). The Covid-19 pandemic and related lockdowns were ongoing during the conduction of this trial (Raman et al., 2021), which might partly explain the high number of dropouts seen for both study arms. We did not track Covid-19 infections due to lack of resources; malaise associated to viral infections may have affected the study outcomes measured, though conceivably in

equal measure between the study arms. Comparatively, the number of participants discontinuing due to adverse events was much lower (17 %), and on the whole we found no difference in the acceptability and tolerability of creatine + CBT against placebo + CBT, indicative of the viability of this intervention. Because of the high dropout rates, however, any findings from this pilot study should be considered with caution, and no clinical recommendations can be made.

In keeping with the established safety profile of creatine (Balestrino and Adriano, 2019; Kreider et al., 2022), we saw no difference in terms of number of patients experiencing any adverse events and their total figure between creatine and placebo. As per previous studies (Hellem et al., 2015), gastrointestinal and muscular complaints were more frequent in the creatine + CBT arm and became less common and troublesome over the course of the trial as tolerance ensued. On the other hand, patients on placebo experienced adverse events that are not usually associated with creatine intake and did so evenly throughout the study. Taken together, these observations strengthen our confidence in participants' concordance with treatment. No severe adverse events, such as manic episodes, occurred during this trial; however, prior RCTs did report manic switches in some patients with bipolar affective disorder (Roitman et al., 2007; Toniolo et al., 2018). Because our study explicitly excluded people with a history of mania, no further conclusion should be made on the safety of creatine use in people with bipolar depression. Furthermore, we did not see any instance of self-harm or suicidal ideation in our relatively large sample of depressed participants, and some similarities have been noticed between creatine and the antidepressant ketamine (Pazini et al., 2020), which also possesses anti-suicidal activity. Nevertheless, this pilot trial was only 8 weeks in duration, so we cannot exclude that longer administrations might lead to a more substantial adverse-event burden, and indeed concerns have been raised regarding chronic use of creatine supplementation, especially for individuals with pre-existing renal disorders (Antonio et al., 2021). Since patients with bipolar and unipolar depression tend to suffer from more physical comorbidities (Croatto et al., 2023), long-term data on the safety of creatine in these populations is necessary.

### 4.1. Limitations

This pilot investigation of the adjunct antidepressant effects of creatine on CBT has several limitations, which emphasise the need to interpret all findings as preliminary and hypothesis-generating. Nonetheless, we were able to complete this proof-of-concept trial in an under-resourced area and in spite of the occurring of untoward factors such as the concomitant Covid-19 pandemic, which supports the feasibility of delivering the study intervention for the care of people with depression in potentially challenging circumstances.

First, our study includes a sizeable yet young (mean age 30.4 years old) and ethnically homogeneous group of people with depression, likely due to the survey sites being based around areas of Dehradun (i.e., Chandrabani, outside Graphic Era Hill University, MDDA Park) where a younger population of people from India can be encountered (i.e., a suburban village, a university, and a park respectively). In line with this, we saw a sample of overall highly-educated (~15 years of education) participants, which could limit the generalisability of our results. We included a wide spectrum of depression severity, ranging from mild to severe as based on PHQ-9 cut-off points (Kroenke et al., 2001). Our findings – though arguably in line with other more diverse RCTs (Kious et al., 2019; Pazini et al., 2019), might therefore not be applicable on a global scale. While we excluded people who had been taking any psychotropic medication over the 8 weeks prior to screening, we did not exclude based on previous use of antidepressant medications or psychotherapy, which may have occurred randomly between study arms but may also affect treatment response.

Second, the amount of missing data from participants who dropped out from the study can limit its internal validity. Despite a larger sample than earlier trials (Kious et al., 2017; Kondo et al., 2011, 2016; Lyoo et al., 2012; Roitman et al., 2007; Toniolo et al., 2017, 2018), we did see high dropout rates, equally distributed between study arms, which may however have caused attrition bias. Still, baseline characteristics were uniformly distributed, and we used a conservative intention-to-treat mixed-effects model ANCOVA that accounts for missing data. Other statistical approaches, employed in some prior trials (Lyoo et al., 2012) such as mixed-effect model repeated measure analysis, may have been suitable; however, we chose to use an ANCOVA of post-treatment effects adjusting for baseline scores to focus on the comparative effects across study arms at a pre-specified time point, which may facilitate pooling of results with several other trials (Kious et al., 2019; Pazini et al., 2019) and emphasise the pilot nature of our study.

Third, some constraints apply to the study treatments and the outcomes measured, which relate to the setting of this study. Patients in the intervention arm experienced adverse events, such as gastroenterological symptoms and muscle pain, known to be more associated with creatine intake. This issue might potentially affect blinding to the intervention, and future studies would benefit from a slower titration (e.g., initial dose 3 mg, then 5 mg as per Lyoo et al., 2012), less likely to elicit significant adverse events at the beginning of treatment. Adherence to treatment was supported via daily reminders, but it was not formally tracked and relied on participants self-report. Participants were free to take creatine/placebo at any time of the day to support compliance – diurnal variations related to this treatment administration may have potentially affected results, but these could be assumed to be at-random in our sample. We used a low-intensity CBT intervention (Bennet-Levy et al., 2010) due to the low-resource setting of this trial, hence results might differ when higher intensity protocols are employed. For similar reasons, we chose to use PHQ-9 depression scores for the primary efficacy outcome as this is a relatively simple, self-reported, yet well-validated instrument to measure severity in a community setting (Kroenke et al., 2001). On the other hand, most previous clinical trials (Kious et al., 2017; Lyoo et al., 2012; Roitman et al., 2007; Toniolo et al., 2018) had employed possibly more objective clinician-rated scales, such as the HAM-D or the Montgomery-Asberg Depression Rating Scale (MADRS), which have however shown comparable validity in routine clinical practice (Zimmerman et al., 2018). Evaluation of participants' neuropsychological functioning, as for certain previous clinical trials (Toniolo et al., 2017), was not possible in this pilot study. We did not measure nor could adjust for baseline dietary habits and related brain creatine level, as this study did not include a mechanistic component that has been advocated for prospective trials (Forbes et al., 2022).

Finally, although the trial protocol has been approved and recorded by the UHRSDA Institutional Ethics Committee (ECR/4263/MH/UK/2020/RR-21), we did not register the protocol on international repositories.

### 4.2. Conclusion

In summary, this hypothesis-generating 8-week trial suggests that the combination of the inexpensive nutraceutical, creatine monohydrate with CBT for depressive disorder is a feasible intervention in under-resourced settings, thanks to its positive efficacy and safety profile, which warrants further investigation of its longer-term benefits and harms.

## Authors contribution

NNS and SD conceptualised and designed the study methodology, and are the guarantor of the project. NNS acquired funding for the trial. SD and TD conducted the investigations and collected the data, which was then validated with NNS and AC. EOG and RDG reviewed the study methodology, curated the data, and conducted the analyses. SD and AC supervised the project. RDG wrote the first draft of the manuscript, which was revised and approved by all authors.

## Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

## Role of the funding source

This study was funded by the Universal Human Rights and Social Development Association (UHRSDA) awarded on the 10th of November 2020, reference ECR/4263/MH/UK/2020/RR-21 (https://www.uhrsda.com/post/institutional-ethics-committee-uhrsda-certificate-for-mr-nima-norbu-sherpa) to NNS.

## Declaration of competing interest

The authors declare none.

## Acknowledgement

None.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2024.10.004.

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