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Beyond Muscle: A Narrative Review of Creatine Monohydrate Supplementation Effects on Cognition, Sleep, and Psychiatric Disorders

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ABSTRACT

Background.

Creatine monohydrate is one of the most widely consumed supplements worldwide. Beyond its well-established role in skeletal muscle bioenergetics, creatine also serves critical functions in the central nervous system, where it acts as a temporal energy buffer, exerts antioxidant and anti-apoptotic effects, and may function as a neuromodulator. These properties raise the

possibility that creatine supplementation may have therapeutic relevance beyond exercise performance.
Aim. The aim of this study was to find and synthesize the available evidence on the effects of creatine monohydrate supplementation on cognitive function in healthy individuals, sleep, and its possible use for psychiatric disorders including major depressive disorder, bipolar disorder, and schizophrenia.
Material and methods.
A narrative review was conducted based on a PubMed/MEDLINE search performed on 13 April 2026, yielding 103 records. Following title and abstract screening, 26 articles were selected for inclusion, comprising randomized controlled trials, open-label studies, and preclinical investigations.
Results.
Cognitive benefits of creatine were most pronounced under conditions of metabolic stress, such as sleep deprivation and hypoxia, with mixed evidence under resting conditions. In psychiatric populations, the strongest evidence is present for unipolar depression, where creatine (3–6 g/day) administered as an adjunct to antidepressant pharmacotherapy or psychotherapy accelerated and potentiated the clinical response in several trials. Preliminary data supported a possible benefit in bipolar depression, while a single trial in schizophrenia found no benefit. The influence of biological sex emerged as a recurring but unresolved moderator of treatment response.
Conclusions.
Creatine monohydrate supplementation shows the greatest therapeutic promise as an adjunctive strategy in unipolar depression. Cognitive effects appear context-dependent, emerging primarily when the brain operates under metabolic stress. Future adequately powered randomized controlled trials with standardized outcome measures are needed to confirm these preliminary findings and to extend the evidence base to other psychiatric conditions.
Key words: creatine monohydrate, cognitive function, major depressive disorder, creatine supplementation, sleep deprivation, nutritional psychiatry

1. INTRODUCTION

Creatine (N-aminoiminomethyl-N-methylglycine) is a naturally occurring guanidino compound synthesized endogenously from the amino acids arginine, glycine, and methionine. It is also obtained exogenously from dietary sources, particularly meat and fish, where it is present at concentrations of approximately 3–5 g per kilogram of raw tissue (Andres et al., 2008; Clarke et al., 2021). Despite being found naturally, to match a typical “loading” dose of 20g/day, one would have to consume approximately 4 kg of meat per day (Clarke et al., 2021). Its supplemental form is most commonly creatine monohydrate, first commercially marketed in the 1990s, but there are other forms, with varying claims of absorption and other properties (Jäger et al., 2011). In recent years creatine has become one of the most widely consumed ergogenic aids worldwide (Clarke et al., 2021; Kreider et al., 2017). Its popularity increased substantially following widespread media coverage of its use by Olympic athletes at the 1992

Barcelona Games (Clarke et al., 2021), and it has since been adopted by both professional and recreational athletes seeking to enhance performance in strength- and power-related activities.

The ergogenic effects of creatine are primarily attributed to its role in the creatine kinase/phosphocreatine system within skeletal muscle, where approximately 95% of the body's total creatine stores reside (Kreider et al., 2017). By serving as a rapidly mobilizable reserve of high-energy phosphate bonds, phosphocreatine enables the local regeneration of adenosine triphosphate (ATP) during brief, high-intensity efforts, thereby improving exercise capacity and facilitating greater training adaptations (Andres et al., 2008; Kreider et al., 2017). Importantly, creatine monohydrate has an established safety profile: the International Society of Sports Nutrition position stand concluded that both short- and long-term supplementation (at doses up to 30 g/day for up to five years) is safe and well-tolerated across a wide range of populations, from children to the elderly (Kreider et al., 2017).

While the muscular effects of creatine supplementation have been extensively documented, the remaining 5% of the body's creatine is distributed among other metabolically active tissues, including the brain, where concentrations reach approximately 10 mM (Pazini et al., 2019). Over the past two decades, a growing body of research has shifted attention beyond muscle, investigating whether exogenous creatine supplementation can influence brain function under both physiological and pathological conditions. In parallel with its bioenergetic role in skeletal muscle, creatine has been found to exert antioxidant, anti-apoptotic, and neuromodulatory effects in the central nervous system (Andres et al., 2008; Lawler et al., 2002; Rae and Bröer, 2015), raising the possibility that supplementation may have therapeutic relevance in neurological and psychiatric disorders — domains in which bioenergetic impairment, oxidative stress, and altered neurotransmission are implicated in the underlying pathophysiology (Pazini et al., 2019).

The present narrative review aims to synthesize the available evidence on the effects of creatine monohydrate supplementation in relation to the central nervous system, with a particular focus on three domains: cognitive function in healthy individuals, sleep, and potential applications in psychiatric disorders including depression, bipolar disorder, and schizophrenia. The review begins with an overview of the proposed mechanisms of creatine action in the brain [Section 3.1], proceeds through the clinical evidence organized by domain [Section 3.2 to Section 3.5], and concludes with a discussion of the factors that may moderate treatment response — including sex, dietary status, dosing regimens, and the relationship to concurrent pharmacotherapy [Section 4].

2. METHODOLOGY

This narrative review was conducted to summarize the current evidence on creatine supplementation on cognition and its potential application in treatment of psychiatric disorders. A literature search was performed using the PubMed/MEDLINE database with search terms such as “creatine”/”creatine supplementation and mental disorders”/”cognition”/”cognitive functions”/”psychiatric disorders”/”psychiatry”. The search was conducted on 13 April 2026 and yielded 103 records. No restrictions on publication date were applied. Articles published in English and Polish were considered for inclusion.

Retrieved records were screened by title and abstract for thematic relevance to creatine supplementation in the context of cognitive functions and psychiatric conditions. Studies were included if they reported on the effects of creatine or phosphocreatine supplementation (either as monotherapy or adjunctive treatment) on cognition, sleep or in populations with psychiatric disorders. Articles unrelated to creatine effects in the brain, indications, conference abstracts without full-text availability, and duplicate publications were excluded. Following the screening process, 26 articles were selected for inclusion in this review. These comprised randomized controlled trials, open-label studies, systematic reviews, meta-analyses, and preclinical studies.

3. RESULTS

3.1. Potential mechanisms of action

Creatine is a guanidino compound that can be either obtained from dietary sources, particularly meat and fish, or endogenously synthesized by the liver, kidney, and pancreas, and to a lesser extent within the brain itself (Andres et al., 2008). While its effects in muscle tissue are well established, creatine also plays a critical role in proper brain functioning. The importance of cerebral creatine is illustrated by the clinical consequences of inborn errors in its synthesis. It has been shown that deficiency of L-arginine-glycine amidino transferase (AGAT) or guanidinoacetate-methyltransferase (GAMT), both of which act as catalyzing enzymes during creatine synthesis in the brain, could cause developmental delays accompanied by intellectual disability, language deficits and (in the case of GAMT deficiency) seizures, with more severe disabilities associated with GAMT deficiency compared to AGAT deficiency (Rae and Bröer, 2015; Stöckler et al., 1994; Bianchi et al., 2000; Item et al., 2001). Creatine taken up from exogenous sources or synthesized in the periphery must cross the blood–brain barrier (BBB) to reach the central nervous system. Because the creatine transporter (SLC6A8) is expressed on the luminal and basal surfaces of microcapillary

endothelial cells but not on the astrocytic endfeet that line these capillaries, creatine transport into the brain may only occur through the limited capillary surface not covered by astrocytic processes (Andres et al., 2008). This restriction in transport likely accounts for the substantially slower uptake and saturation of creatine in the brain compared with skeletal muscle (Andres et al., 2008; Ipsiroglu, et al., 2001).

There are multiple proposed mechanisms explaining the role of creatine in the central nervous system. The primary and best-understood role of creatine in the brain is its function as an acceptor of high-energy phosphate, mediated by the creatine kinase (CK) reaction that enables fast, reversible exchange between ATP and the phosphorylated form of creatine, phosphocreatine (Rae and Bröer, 2015). Phosphocreatine serves as a rapidly accessible energy reserve, allowing local in situ regeneration of ATP at sites distant from mitochondrial production (Andres et al., 2008). Therefore, creatine acts as an easy-to-access "energy bank", which allows linking sites of ATP generation with sites of consumption. This function is especially critical in the central nervous system, where the brain accounts for approximately 20% of the body's resting metabolic expenditure despite comprising only 2% of total body mass (Rae and Bröer, 2015).

Beyond its standard bioenergetic role, creatine was found to have anti-apoptotic effects and antioxidant properties via direct scavenging of reactive oxygen species or reducing the production of reactive oxygen species generated in mitochondria (Andres et al., 2008; Sestili et al., 2011). Lawler et al. (2002) demonstrated that creatine directly scavenges charged reactive species, including the superoxide anion, peroxynitrite, and the $ABTS^{+}$ cation radical, though notably it did not significantly quench uncharged oxidants such as hydrogen peroxide or lipid peroxides. Additionally, creatine appears to reduce mitochondrial reactive oxygen species production indirectly, by stimulating mitochondrial creatine kinase–dependent ADP recycling, which maintains tight coupling of the respiratory chain (Andres et al., 2008; Meyer et al., 2006). These protective effects extend to the mitochondrial genome, where creatine supplementation has been shown to attenuate oxidative damage to mitochondrial DNA, potentially contributing to the prevention of pathologies linked with mitochondrial mutagenesis (Guidi et al., 2008).

There has also been evidence that creatine has a positive effect on cerebral vasculature, improving circulation in the brain (Andres et al., 2008; Clarke et al., 2021). Creatine kinase isoenzymes and the creatine transporter are expressed in vascular endothelial cells (Clarke et al., 2021; Decking et al., 2001). Preliminary clinical data suggest that creatine supplementation may improve microvascular reactivity, capillary density, and endothelial

function, possibly through antioxidant-mediated preservation of nitric oxide bioavailability (Clarke et al., 2021). An effect of creatine on the vasodilatory response in the brain has also been proposed as a possible mechanism underlying its neuroprotective action against cerebral ischemia, independent of changes in the brain energy metabolite levels (Andres et al., 2008; Prass et al., 2007). In addition to these properties, emerging evidence suggests that creatine may function as a neuromodulator in the brain. In vitro experiments have demonstrated that creatine is released from neurons in an action potential–dependent manner, with this release being blocked by tetrodotoxin and by the absence of extracellular calcium, which is consistent with exocytotic neurotransmitter release (Almeida et al., 2006; Pazini et al., 2019). Furthermore, there is moderately strong, though not yet conclusive, evidence that creatine modulates N-methyl-D-aspartate (NMDA) receptor activity, possibly through an interaction at the polyamine binding site (Rae and Bröer, 2015; Oliveira et al., 2008).

These diverse mechanistic properties converge on pathways that are directly relevant to the pathophysiology of psychiatric disorders. Bioenergetic impairments, which include reduced neuronal ATP production rates and altered phosphocreatine metabolism, have been consistently documented in depression and are related to the severity of depressive symptoms (Rae and Bröer, 2015; Pazini et al., 2019). Preclinical studies have further shown that stress paradigms used to model depression alter creatine kinase activity and creatine levels in brain regions implicated in mood regulation, including the prefrontal cortex and hippocampus, while several classes of antidepressants restore creatine kinase activity in these regions (Pazini et al., 2019). Beyond restoring cellular energy homeostasis, creatine also appears to modulate neurotransmitter systems central to current theories of depression: its antidepressant-like effects in animal models depend on the activation of dopaminergic (D_1 and D_2), serotonergic (5-HT_1A), and noradrenergic (α_1) receptors, and are potentiated by co-administration with conventional antidepressants targeting these systems (Pazini et al., 2019; Cunha et al., 2012; 2013a; 2013b). Notably, creatine activates the PI3K/Akt/mTOR signaling cascade and increases hippocampal levels of PSD-95 and BDNF - a mechanism similar in several features to the rapid antidepressant response to ketamine (Pazini et al., 2019).

3.2. Cognitive functions, mood and sleep

3.2.1 Effects on cognitive performance under resting conditions

The question of whether creatine supplementation enhances cognition in healthy, rested individuals has been addressed by a growing number of trials, though the evidence remains heterogeneous.

The largest study to date (Sandkühler et al., 2023) employed a double-blind, placebo-controlled crossover design with 5 g/day of creatine monohydrate for six weeks and a five-week washout. There were two primary outcomes in this study: a timed subtest of Raven's Advanced Progressive Matrices (RAPM), measuring abstract reasoning, and the Wechsler auditory Backward Digit Span (BDS), measuring working memory. These outcomes were supplemented by eight exploratory tasks probing attention, task switching, memory, inhibitory control and verbal fluency. Bayesian analysis supported a small beneficial effect of creatine; the BDS result bordered on significance, whereas in the case of RAPM there were no significant differences between groups. Notably, roughly half the participants were vegetarians and half omnivores, yet no interaction between dietary status and supplementation emerged — in contrast to earlier findings suggesting that vegetarians, who have lower endogenous creatine stores, might benefit preferentially.

That earlier finding came from Benton and Donohoe (2011), who gave 121 young women either 20 g/day of creatine or placebo for five days. Creatine supplementation did not influence verbal fluency or vigilance; however, it significantly improved memory performance in the vegetarian subgroup but not in omnivores, consistent with the hypothesis that lower baseline brain creatine creates greater room for augmentation. Irrespective of dietary status, creatine also reduced the variability of choice reaction times, pointing to a stabilizing effect on attentional processes that is independent of baseline creatine stores.

A study by McMorris et al. (2007a) targeted healthy elderly individuals (mean age 76.4 years) using a high-dose loading protocol (20 g/day for one week) – population different than in most other studies, which tend to focus on young volunteers. Compared with a placebo-only control group, the creatine-supplemented group showed significant within-group improvement on tasks tapping short-term storage and retrieval: forward verbal recall, forward and backward spatial recall and long-term memory recall. Backward number recall, however, did not improve. Because this task requires not merely holding information but actively reorganizing it, it recruits the central executive and activates substantially larger cortical networks (Sun et al., 2005); the authors suggested that the creatine-related increase in brain energy reserves may have been insufficient for the most demanding manipulative operations. The authors concluded that creatine aids cognition in the elderly, although the small sample and the absence of a crossover or extended maintenance phase limit generalization.

In contrast, two studies using creatine combined with guanidinoacetic acid (GAA) did not replicate cognitive gains. Seper et al. (2021) administered a GAA–creatine mixture to 21 healthy elderly individuals (mean age 69.6 years) in an eight-week crossover trial. Although

brain and muscle creatine levels increased significantly, cognitive performance assessed by the Montreal Cognitive Assessment (MoCA) did not differ from placebo. Zanini et al. (2025) gave 19 healthy young adults 2 g creatine + 2 g GAA daily for seven days and found no significant differences in Symbol Digit Modalities Test, Trail Making Test-B, or Stroop Color and Word Test scores. However, prefrontal cerebral oxygen saturation rose significantly during phases of rest, cognitive testing and recovery in the creatine–GAA group. This hints towards a hemodynamic change that may be mechanistically relevant even in the absence of immediate performance gains.

Some other studies did not find direct improvements in cognitive abilities after supplementation of creatine. A longer supplementation period was tested by Rawson et al. (2008), who gave 22 young non-vegetarian adults a low maintenance dose (0.03 g/kg/day) for six weeks. No significant effects of group, time, or their interaction emerged for simple reaction time, code substitution (immediate and delayed), logical reasoning, mathematical processing, running memory, or memory recall. Similarly, Fernandez-Garrido et al. (2026) embedded creatine supplementation (3 g/day for 16 weeks) within a resistance-training programs for a larger group of older adults (mean age 68.2 years). Both training modalities — elastic-band and aquatic-based — significantly improved Trail Making Test A and B scores, but creatine co-administration did not confer additional cognitive benefit. Creatine alone did, however, reduce markers of oxidative stress (F2-isoprostanes) and systemic inflammation (TNF-α) and improve perceived general health on the Short-Form Health Survey 36 (SF-36), suggesting that its effects may be context-dependent and more evident under metabolic stress than in rested, adequately nourished individuals.

While creatine monohydrate is the most popular form of creatine, one study examined a different creatine formulation. Ling et al. (2009) supplemented 34 young adults (12 women; none vegetarian) with 5 g/day of creatine ethyl ester (CEE) or placebo for 15 days and assessed memory scanning, number-pair matching, sustained attention, an arrow flanker task, and Raven's matrices. Performance appeared to improve on several measures in the creatine group. The authors themselves noted, however, that no objective measure of compliance was obtained (no participant returned unused materials) and called for replication with verified adherence.

Similarly, the interaction of creatine with other ergogenic compounds was explored by Mabrey et al. (2024), who administered creatine nitrate (5 g/day), caffeine (400 mg/day), their combination, or placebo to 12 resistance-trained men in a crossover design. Cognitive function was assessed with the Stroop Word–Color Test. Only the combined condition

(creatine nitrate + caffeine) significantly improved performance on the Stroop interference subtest, and post hoc analysis showed the combination was superior to creatine nitrate alone; neither supplement individually reached significance against placebo. These findings suggest a synergistic interaction on cognitive interference processing, though the small sample and the use of creatine nitrate rather than monohydrate limit direct comparability with the broader literature**.**

3.2.2 Cognitive protection under metabolic stress

A separate line of evidence suggests that creatine's cognitive effects become more apparent when the brain operates under energetic strain. This pattern is consistent with its role as a phosphagen buffer. McMorris et al. (2006) supplemented 19 young adults (creatine n = 10; placebo n = 9) with 20 g/day of creatine monohydrate for seven days and then imposed 24 hours of sleep deprivation with mild exercise. At 24 hours, the creatine group showed significantly less deterioration than placebo on random movement generation, choice reaction time and static balance, and also preserved mood state (shortened Profile of Mood States (POMS)). However, no group differences were apparent at 6 or 12 hours, and verbal and spatial short-term memory did not differ at any time point. The effect thus appeared selectively at the most demanding interval and on tasks drawing heavily on prefrontal executive resources. A similar threshold pattern was also reported by McMorris et al. (2007b) at 36 hours of sleep deprivation with moderate exercise.

Turner et al. (2015) applied the same logic to oxygen deprivation. Fifteen healthy adults were supplemented with creatine (20 g/day for 7 days) or placebo in a crossover design, after which 90 minutes of normobaric hypoxia (10% O_2) was imposed. Magnetic resonance spectroscopy (MRS) confirmed a mean 9.2% increase in neural creatine. Hypoxia significantly impaired a range of neurocognitive domains assessed with a standardized computerized battery (CNS Vital Signs); creatine supplementation restored performance specifically in complex attention, executive function, cognitive flexibility and the overall neurocognitive index. Corticomotor excitability, assessed via transcranial magnetic stimulation, also increased under creatine. This was the first demonstration that dietary creatine can protect human brain function against an acute energetic insult, and it complements the sleep-deprivation findings in framing creatine as a reserve fuel that becomes consequential when ordinary oxidative ATP supply falters.

3.2.3 Effects on mood

The evidence for a direct effect of creatine on mood in non-clinical populations is limited. Furtado et al. (2024) assessed mood state using the 24-item Brunel Mood Scale (BRUMS) as

a secondary endpoint in 12 strength-trained men who received a five-day creatine loading protocol (20 g/day) or placebo. No significant differences in vigour or fatigue were observed between conditions or between pre- and post-supplementation time points. Given the small sample and the fact that participants were healthy, well-trained individuals without baseline mood disturbance, the absence of an effect is perhaps unsurprising and might not be extrapolated to clinical psychiatric populations, where the bioenergetic rationale for creatine's mood-enhancing properties rests on a different metabolic substrate. It is also worth noting that self-report instruments such as the BRUMS may lack the sensitivity to detect subtle mood shifts in an already euthymic, physically active cohort. This consideration applies broadly to mood assessment in non-clinical supplementation studies.

3.2.4 Creatine and Sleep

Creatine's role as a cellular energy buffer has prompted interest in two related questions: whether supplementation can protect cognition against the demands of sleep deprivation, and whether it can improve sleep quality itself.

The earliest evidence addressed the first question. McMorris et al. (2007b) supplemented 20 male volunteers (two groups of ten) with creatine monohydrate (5 g four times daily) or placebo for seven days, then assessed cognition at baseline and after 18, 24 and 36 hours of sleep deprivation combined with intermittent moderate-intensity exercise. Creatine conferred no broad cognitive advantage: the groups differed only on a central executive task, and only at 36 hours, when the metabolic and psychological demands were greatest. Within the creatine group this task nonetheless improved linearly across the protocol, whereas the placebo group showed no change. This suggests that creatine's benefit emerges selectively under the most taxing, energy-demanding conditions.

Additional findings emerged from a study by Gordji-Nejad et al. (2026), which administered a single dose of creatine monohydrate (0.2 g/kg) or placebo to 29 healthy adults (17 women) during 21 hours of sleep deprivation, testing cognition at 3, 5.5 and 7.5 hours post-dose. Creatine attenuated the deprivation-induced decline across a broader range of domains than in the earlier study (Gordji-Nejad et al., 2024) including logical and numerical reasoning, language-related processing speed, and the Psychomotor Vigilance Test (PVT). It was noted that the effect was more noticeable in women than men. The effect, although present at this lower dose, was less pronounced than that reported for the 0.35 g/kg dose in the authors' earlier work (Gordji-Nejad et al., 2024), consistent with a dose-dependent action in which a single bolus transiently replenishes the brain's energy reserves against the cellular stress of sleep loss.

The second question, sleep quality under ordinary conditions rather than deprivation, was addressed by Ben Maaoui et al. (2025). In a double-blind crossover trial, 14 physically active men completed a seven-day creatine loading protocol (20 g/day) or placebo alongside their usual training. Creatine significantly improved self-rated sleep quality (Sleep Subjective Quality scale) and performance on the digit cancellation test, a measure of sustained attention. Objective sleep metrics derived from wrist actigraphy, however, did not differ between conditions. This dissociation between self-rated sleep and wrist actigraphy hints that further studies assessing effects of creatine supplementation on sleep, with more objective measurements, are needed.

3.3. Creatine supplementation in psychiatry

3.3.1. Major Depressive Disorder (MDD)

Convergent evidence links depressive disorders to disturbances in cerebral energy metabolism, and creatine, acting as a central buffer of the brain's high-energy phosphate system, has accordingly been proposed as a metabolic augmentation strategy. Consistent with this rationale, phosphocreatine concentrations are reduced in the brains of severely depressed patients (Kato et al., 1992). The first clinical signal came from an open-label add-on study by Roitman et al. (2007), in which ten patients with treatment-resistant depression (eight unipolar, two bipolar) received creatine monohydrate for four weeks (3 g/day in week 1, then 5 g/day). Among the seven unipolar patients retained in the analysis, scores on the Hamilton Depression Rating Scale 21-item version (HAM-D), Hamilton Anxiety Scale (HAS) and Clinical Global Impression (CGI) improved significantly, with most of the benefit apparent within the first week and 71% (5/7) achieving a >50% reduction in HAM-D. Both bipolar patients, however, developed (hypo)mania and were withdrawn. This presents a safety concern further considered in detail in the section on bipolar depression. Two further observations support a causal interpretation: symptoms transiently worsened when the dose was raised to 5 g/day and improved again on return to 3 g/day, hinting at an inverted U-shaped dose–response, and several completers relapsed after discontinuation but responded again on rechallenge.

These preliminary findings were substantiated by the first randomized, double-blind, placebo-controlled trial (Lyoo et al., 2012). Fifty-two women with MDD, free of psychotropic medication for at least eight weeks, received escitalopram plus either creatine monohydrate (5 g/day) or placebo over eight weeks, of whom 39 completed. Creatine augmentation yielded significantly greater improvement on the HAM-D, which was evident as early as week 2,

indicating an accelerated onset of response, with parallel gains on the Montgomery-Åsberg Depression Rating Scale (MADRS). Remission (HAM-D ≤ 7) was reached by 52.0% of the creatine group versus 25.9% on placebo, while premature discontinuations and adverse events did not differ between arms.

The neurobiological correlates of this response were examined in the imaging arm of the same cohort (Yoon et al., 2016). Relative to placebo, creatine augmentation not only produced greater clinical improvement but also significantly increased prefrontal N-acetylaspartate and strengthened rich-club connectivity of the structural brain network. N-acetylaspartate is a marker of neuronal integrity that was reduced at baseline in MDD, suggesting causal connection between biochemistry and clinical presentation. Additionally, these metabolic and network changes offer a plausible mechanistic bridge between creatine's bioenergetic action and its antidepressant effect.

Target engagement was probed more directly in a dose-ranging ^{31}P-MRS study of adolescent females with SSRI-resistant depression (Kondo et al., 2016). Changes in brain metabolism were assessed by observing change in ^{31}P-MRS metabolites, such as phosphocreatine (PCr), beta-nucleoside triphosphate (β-NTP; largely adenosine triphosphate, ATP) and inorganic phosphate (Pi). Changes of these metabolites were found to correlate with responsiveness to selective serotonin reuptake inhibitor (SSRI) medications (Renshaw et al., 2001; Iosifescu et al., 2008). Study participants received placebo or creatine monohydrate at 2, 4 or 10 g/day for eight weeks. Frontal-lobe phosphocreatine rose by 4.6%, 4.1% and 9.1% across the three active doses, against a 0.7% decline on placebo; although these between-group differences did not reach significance, frontal phosphocreatine was inversely correlated with depression severity across the whole sample ($p = 0.02$), linking the bioenergetic target to a clinical signal.

A complementary approach paired creatine with serotonergic precursor loading (Kious et al., 2017). In this open-label trial, 15 women with SSRI/Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)-resistant MDD received creatine monohydrate (5 g/day) together with 5-hydroxytryptophan (100 mg twice daily) for eight weeks, and 12 completed. Mean HAM-D fell from 18.9 to 7.5 (−60%), with concordant improvements on the MADRS (25.4 to 9.0), Beck Anxiety Inventory (BAI; change from 22.7 to 9.3) and Clinical Global Impression-Severity (CGI-S) (4.1 to 1.9; all $p < 0.00001$) and no serious treatment-related adverse events. The absence of a placebo arm nonetheless limits interpretation.

Recently, Sherpa et al. (2025) focused on psychological rather than pharmacological intervention, adding creatine monohydrate (5 g/day) or placebo to cognitive-behavioral therapy in 100 community patients (50 women) with depression in an under-resourced setting.

Although Patient Health Questionnaire-9 (PHQ-9) scores declined in both arms, the reduction was significantly greater with creatine with comparable tolerability and no manic switches. Unlike the earlier, predominantly female-only trials and several preclinical models, efficacy was not modified by sex — a finding that, together with the larger mixed-sex sample, strengthens the generalizability of the evidence.

Not every trial has replicated these benefits. In a dose-finding RCT, Nemets and Levine (2013) added creatine (5 or 10 g/day) or placebo to ongoing antidepressants in 18 patients (14 women) who had failed to respond to three weeks of treatment, and found no overall advantage of either dose over placebo on the HAM-D or CGI-S; only a small subgroup of women showed a rapid early response, with two patients achieving a >50% HAM-D reduction within two weeks. Likewise, Alves et al. (2013) observed no antidepressant effect of creatine in apparently healthy older women: over 24 weeks, Geriatric Depression Scale scores fell significantly in the strength-training groups (with or without creatine) but not with creatine supplementation alone, indicating that the mood benefit was driven by exercise rather than creatine and pointing to limited efficacy in the absence of clinical depression.

3.3.2. Bipolar Disorder

Creatine augmentation of the depressive phase of bipolar disorder represents a logical extension of the unipolar evidence, as bipolar depression shares much of its symptom profile with MDD while arising from distinct pathophysiology. The metabolic rationale is supported by phosphorus MRS studies reporting reduced phosphocreatine across the whole brain in bipolar II disorder (Kato et al., 1994) and in frontal gray matter of adolescents with bipolar I disorder in manic or euthymic states (Dudley et al., 2016), complemented by findings of decreased total creatine in the hippocampus (Yüksel et al., 2015).

This hypothesis was tested in a randomized, double-blind, placebo-controlled, proof-of-concept trial in which 35 patients with bipolar disorder type I or II in a depressive episode (DSM-IV) received either creatine monohydrate 6 g/day or placebo as an adjunct to their ongoing medication for six weeks (Toniolo et al., 2018). The primary outcome, defined as change in the Montgomery–Åsberg Depression Rating Scale (MADRS), did not differ significantly between groups in the intention-to-treat analysis , nor did changes on the HAM-D, Young Mania Rating Scale (YMRS), CGI-S, or Functioning Assessment Short Test (FAST). Analysis of categorical outcomes among the 35 randomized patients, however, favored creatine: rates of partial response (82.4% vs. 38.4%; $p = 0.015$) and of remission, defined as a MADRS score ≤ 12 (52.9% vs. 11.1%; $p = 0.012$), were significantly higher in the creatine group, and the superiority in remission persisted among completers (66.7% vs.

18.2%; p = 0.036). Notably, a post hoc analysis restricted to female patients found no significant advantage for creatine, contrasting with the female-specific effects reported in unipolar depression.

Cognitive outcomes from the same trial were reported separately (Toniolo et al., 2017): among the 18 patients who underwent neuropsychological assessment, creatine augmentation was associated with a significant improvement in verbal fluency (FAS test) relative to placebo, with no significant differences on the remaining measures (Wisconsin Card Sorting Test, Digit Span, Stroop Color–Word Test, Rey–Osterrieth complex figure).

The safety profile in this study was favorable. All adverse events were mild and transient, and no abnormalities in renal function markers were observed. However, two patients in the creatine group switched to hypomania or mania early in the trial and were withdrawn. Although based on few cases, this signal underscores the principal safety concern that attends any antidepressant strategy in bipolar depression and tempers the interpretation of creatine's apparent benefit on remission. Taken together, these findings suggest that creatine may hold promise as an adjunctive treatment for the depressive phase of bipolar disorder. It may offer the possibility of relieving a symptom profile that overlaps substantially with unipolar depression despite a distinct underlying pathophysiology. However, there is a need for larger trials, both to confirm efficacy and to characterize the risk of affective switch.

3.3.3. Schizophrenia

Evidence for creatine in schizophrenia is limited and, to date, negative. The rationale parallels that in mood disorders: hypofrontality and ^{31}P-MRS findings of reduced ATP in frontal and left temporal regions have implicated impaired cerebral energy metabolism in the disorder, raising the possibility that enhancing brain bioenergetics might benefit hypometabolic areas and their associated negative and cognitive symptoms (Kaptsan et al., 2007). One study examined this in a randomized, double-blind, placebo-controlled crossover trial of twelve patients with stable, chronic schizophrenia (DSM-IV; no substantial change in clinical presentation over the preceding six months) selected for prominent negative and cognitive symptoms (Kaptsan et al., 2007). Each patient received both creatine monohydrate (3 g/day for the first month, then 5 g/day for two months) and placebo for three months apiece in randomized order; ten patients completed the study. Creatine was not superior to placebo on any clinical measure (Positive and Negative Syndrome Scale (PANSS) and its subscales, CGI-Severity, Abnormal Involuntary Movement Scale (AIMS)) or on any neuropsychological outcome, whether analyzed across the full crossover or as a parallel-group comparison of the

first three months. Supplementation was well tolerated, with nausea being the most common side effect.

The authors interpreted this null result cautiously rather than as a definitive refutation, noting the small sample, the restriction to chronically ill patients, and a dose and duration that may have been insufficient. They further speculated that the reduced brain creatine kinase activity reported in schizophrenia (Burbaeva et al., 2003) might limit patients' capacity to convert supplemental creatine into phosphocreatine, offering a possible mechanistic explanation for the absence of effect.

4. DISCUSSION

The present narrative review synthesizes the available evidence on the efficacy of creatine supplementation across cognitive, sleep-related, and psychiatric domains. Based on the studies reviewed, there is moderate evidence that creatine can improve cognitive function, though the magnitude and consistency of these effects depend heavily on context. The most pronounced cognitive benefits were observed under conditions of metabolic stress, such as sleep deprivation (McMorris et al., 2006) and hypoxia (Turner et al., 2015), suggesting that creatine may be more effective at protecting existing cognitive capacity under physiological challenge than at enhancing it per se. This pattern aligns with the known bioenergetic role of the creatine kinase/phosphocreatine system as a temporal energy buffer: under metabolic stress, increased demand for ATP may deplete phosphocreatine reserves, creating a functional deficit that exogenous creatine supplementation can compensate (Rae and Bröer, 2015). Evidence for cognitive augmentation in healthy, rested individuals is mixed: some studies have reported improvements in working memory and abstract reasoning (Sandkühler et al., 2023; Benton and Donohoe, 2011; McMorris et al., 2007a), whereas others found no significant benefit (Seper et al., 2021; Rawson et al., 2008; Fernandez-Garrido et al., 2026). A comparable pattern emerges in the literature concerning sleep, where creatine effects appear more robust in protecting against the cognitive and affective consequences of sleep deprivation (McMorris et al., 2007b; Gordji-Nejad et al., 2026) than in enhancing sleep quality under normal conditions. Nonetheless, a subjective improvement in sleep quality has been reported (Ben Maaoui et al., 2025), which may warrant further investigation.

Similar conclusions can be drawn regarding the application of creatine supplementation in psychiatric disorders. The strongest body of evidence points to unipolar depression. The reviewed studies suggest that creatine may serve as an effective augmentation strategy for standard antidepressant pharmacotherapy. This is supported mechanistically by the known

actions of creatine in the central nervous system, including restoration of impaired phosphocreatine metabolism in depression (Kondo et al., 2016), modulation of monoaminergic and glutamatergic neurotransmitter systems, and activation of the PI3K/Akt/mTOR signaling cascade — a pathway that parallels several features of the rapid antidepressant response to ketamine (Pazini et al., 2019). Preclinical evidence reinforces the augmentation rationale directly: in animal models, sub-effective doses of creatine co-administered with fluoxetine, paroxetine, citalopram, sertraline, or reboxetine produced synergistic antidepressant-like effects in the tail suspension test (Cunha et al., 2013a; 2013b), suggesting that creatine engages complementary mechanisms that potentiate classical monoaminergic antidepressants. Notably, the rapid onset of clinical improvement observed in the largest randomized trial (Lyoo et al., 2012), where benefits over placebo emerged as early as week two, echoes this profile and distinguishes creatine augmentation from the typical four-to-six-week latency of conventional antidepressant treatment. Nevertheless, the findings remain non-conclusive, and further adequately powered studies are required.

The evidence for other psychiatric disorders is considerably more limited. Preliminary data suggest a potential benefit of creatine in the depressive phase of bipolar disorder, with one randomized controlled trial reporting significantly higher remission rates in the intention-to-treat analysis (Toniolo et al., 2018). However, the occurrence of manic or hypomanic switches in some patients following initiation of creatine supplementation warrants caution and underscores the need for careful evaluation of the safety profile in this population. This destabilizing effect may reflect the dual-edged nature of bioenergetic augmentation in bipolar disorder: while restoring energy metabolism in the depressive phase may be therapeutically beneficial, the same enhancement could lower the threshold for manic switching in susceptible individuals, consistent with the mitochondrial hyperactivity model of mania (Yüksel et al., 2015; Rae and Bröer, 2015). In schizophrenia, the available evidence is limited to a single small trial that found no benefit (Kaptsan et al., 2007). The absence of effect in schizophrenia, contrasting with the positive findings in affective disorders, may relate to the reduced brain creatine kinase activity reported in this condition (Burbaeva et al., 2003), which could limit patients' capacity to convert supplemental creatine into phosphocreatine and thereby attenuate its downstream effects. In both cases, larger, standardized trials are needed for more definitive conclusions.

The heterogeneity of the studied populations represents an important consideration. Across multiple studies, the effects of creatine supplementation appear to be more pronounced in women than in men. This sex-specific pattern was most evident in unipolar depression, where

several studies reporting positive results enrolled exclusively or predominantly female participants (Lyoo et al., 2012; Kondo et al., 2016; Kious et al., 2017). However, in a trial examining creatine augmentation of cognitive-behavioral therapy for depression (Sherpa et al., 2025), no moderation by sex was observed, and a post hoc analysis of the bipolar disorder trial (Toniolo et al., 2018) revealed that the creatine advantage was absent in the female-only subgroup, presenting an interesting reversal of the pattern seen in unipolar depression. In animal models, this sex-dependent response has biological correlates: Allen et al. (2012) demonstrated that the antidepressant-like effect of creatine in the forced swim test was selective for female rats, and that creatine kinase activity fluctuated in synchrony with estradiol levels across the estrous cycle, suggesting a hormonal mechanism by which estrogen may modulate the creatine kinase/phosphocreatine system and thereby influence treatment response. It therefore remains an open question whether the female-predominant clinical findings reflect a genuine biological effect, which may be mediated by estrogenic modulation of creatine kinase, or indicate a selection artefact arising from preferential recruitment of female participants.

Regarding other population-level variables, the effects appear less consistent. The comparison between vegetarians and omnivores yields mixed evidence. The "depleted baseline" hypothesis posits that individuals with lower endogenous creatine stores — such as vegetarians, who have reduced muscle creatine levels (Delanghe et al., 1989; Rae and Bröer, 2015) — may derive greater benefit from supplementation due to a larger capacity for augmentation. However, this reasoning may not extend straightforwardly to the brain: Solis et al. (2014) demonstrated that brain creatine concentrations in vegetarians are comparable to those in omnivores, suggesting that cerebral creatine homeostasis is maintained independently of dietary intake, possibly through endogenous synthesis within the central nervous system. While Benton and Donohoe (2011) found that creatine improved memory selectively in vegetarians, the largest study to date (Sandkühler et al., 2023) found no interaction between dietary status and supplementation effects, leaving the hypothesis unresolved. In geriatric populations, the evidence for cognitive or mood-related benefits is weak. Psychiatric effects of creatine were observed irrespective of age, but in the context of disease (specifically depression) rather than in healthy ageing.

The dosing regimens employed across the reviewed studies varied considerably, yet some consistent patterns emerges when stratified by context. In psychiatric applications, effective doses ranged from 3 to 6 g/day administered over four to eight weeks (Roitman et al., 2007; Lyoo et al., 2012; Kondo et al., 2016; Toniolo et al., 2018), whereas cognitive studies

conducted under acute metabolic stress typically employed short loading protocols of 20 g/day for five to seven days (McMorris et al., 2006; Turner et al., 2015). This divergence may reflect the anatomical constraints on cerebral creatine uptake discussed in the mechanisms section: because the creatine transporter is not expressed on astrocytic endfeet lining brain microcapillaries, saturation of brain creatine stores is substantially slower than in skeletal muscle (Andres et al., 2008), potentially necessitating higher initial doses when rapid cognitive effects are sought. Conversely, the lower daily doses effective in depression trials suggest that prolonged supplementation at maintenance levels may be sufficient to achieve therapeutically meaningful increases in cerebral phosphocreatine over weeks. Notably, the dose-ranging data from Kondo et al. (2016), where the strongest clinical response was observed at 2 g rather than at the higher 4 g or 10 g doses, hints at a possible non-linear dose–response relationship that may be explored in further studies.

With respect to the relationship between creatine and antidepressant pharmacotherapy, two distinct augmentation models are present in the literature. In the first, creatine was initiated concurrently with a selective serotonin reuptake inhibitor, as in the trial by Lyoo et al. (2012), where co-administration with escitalopram produced measurable improvement as early as week two, a latency substantially shorter than the four-to-six-week onset typically expected with SSRI monotherapy. In the second model, creatine was added to an established but insufficiently effective antidepressant regimen, as in the studies by Kondo et al. (2016) and Kious et al. (2017), both of which reported clinically meaningful symptom reduction in patients who had not responded adequately to prior SSRI treatment alone. These clinical observations are reinforced by preclinical evidence demonstrating synergistic antidepressant-like effects when sub-effective doses of creatine were co-administered with multiple classes of monoaminergic antidepressants in animal models (Cunha et al., 2013a; 2013b; Pazini et al., 2019). Taken together, these findings suggest that creatine supplementation may be most promising not as a standalone intervention but as an adjunctive strategy capable of both accelerating and potentiating the response to conventional antidepressant treatment, although this conclusion rests on a small number of trials and requires confirmation in larger, methodologically rigorous studies.

Several limitations of this review and of the available evidence base should be acknowledged. First, this is a narrative review based on a search of a single database (PubMed/MEDLINE) with language restrictions to English and Polish, without the formal screening protocols, risk-of-bias assessment, or PRISMA-compliant reporting that characterize systematic reviews. It is therefore possible that relevant studies indexed in other databases or published in other

languages were not captured, and the conclusions drawn here should be interpreted accordingly. Second, the included studies are characterized by small sample sizes, considerable heterogeneity in study design, dosing protocols, outcome measures, and creatine formulations, as well as uniformly short follow-up periods, all of which limit cross-study comparability and preclude formal meta-analysis. Third, several psychiatric conditions for which a bioenergetic rationale exists — including post-traumatic stress disorder, anxiety disorders, and substance use disorders — have not been investigated in clinical trials of creatine supplementation, and the generalizability of the present findings to these conditions remains unknown.

5. CONCLUSIONS

The available evidence suggests that creatine monohydrate supplementation can improve cognitive function primarily under conditions of metabolic stress, such as sleep deprivation and hypoxia, rather than in rested, well-nourished individuals. However, some evidence for cognitive benefits under normal conditions also exists and warrants further investigation in larger-scale trials. In psychiatric populations, the strongest evidence is present for unipolar depression, where creatine at doses of 3–6 g/day, used as an adjunct to antidepressant pharmacotherapy or psychotherapy, has shown the potential to accelerate and potentiate the clinical response. Preliminary data also support a possible benefit in bipolar depression, although the risk of manic or hypomanic switching demands careful safety evaluation. Evidence in schizophrenia remains insufficient. The influence of biological sex on treatment response is a recurring but unresolved aspect. Future research should prioritize adequately powered, randomized controlled trials with standardized outcome measures, extend the evidence base to psychiatric conditions not yet investigated, and systematically address dose–response relationships, optimal treatment duration, and long-term safety.

DISCLOSURE

Artificial intelligence tools were used solely as a linguistic aid to improve English language clarity and formatting. The scientific content, literature selection, interpretation of results and final manuscript preparation were performed by the authors.

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