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THERAPEUTIC POTENTIAL OF CREATINE IN PSYCHIATRY: FROM NEUROBIOLOGY TO CLINICAL APPLICATIONS

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ABSTRACT

Mental disorders such as depression, bipolar disorder, schizophrenia, and anxiety are difficult to treat due to their complex neurobiological substrates. Traditional treatments, including pharmacotherapy and psychotherapy, are poor in alleviating symptoms in the majority of patients, where other forms of intervention have been sought. Creatine supplementation, which has been shown to previously improve sports performance, has been looked upon in this context as a form of treatment. Creatine plays a critical role in cellular energy metabolism, particularly in the brain, where it may be useful in the alleviation of energy deficits, oxidative stress, and mitochondrial dysfunction. This review consolidates available information on mechanisms of creatine action, clinical trials, and therapeutic implications in psychiatric disorders and discusses its well-established application in sports with its physiological and molecular effects. Specifically, we address creatine's influence on energy metabolism, neuroprotection, neurotransmitter modulation, and synaptic plasticity. The evidence shows creatine to be a potentially valuable adjunctive treatment, particularly in depression and affective disorders; however, more research is called for to elucidate its whole therapeutic value and develop optimal dosing regimens in heterogeneous patient populations.

KEYWORDS

Creatine, Psychiatric Disorders, Depression, Bipolar Disorder, Schizophrenia

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Introduction

Psychiatric illnesses such as depression, bipolar disorder, schizophrenia, and anxiety constitute a serious worldwide public health burden with complex and interposing neurobiological impairments. Conventional treatments such as pharmacotherapy and psychotherapy are not adequate enough to cure all patients and offer incomplete remission or drug resistance to a few patients. Previous research has therefore concentrated on more novel therapies, like dietary supplements, e.g., creatine, which is well-documented to improve physical function but less for its use in psychiatry. Creatine's potential to augment cellular energy metabolism, i.e., in the brain, makes it plausible to have an impact to improve underlying deficits in psychiatric illness, e.g., mitochondrial dysfunction and oxidative stress. The aim of this review is to provide an overview of the current evidence on creatine supplementation in such disorders, their mechanisms, clinical efficacy, and therapeutic potential, and highlight the gaps to be filled.

Creatine in Psychiatric Disorders

Creatine is a structurally related conditionally essential amino acid analogue, which mediates phosphocreatine-mediated resynthesis of ATP, particularly in energy-demanding tissues like the brain. Psychiatric diseases like depression, bipolar disorder, schizophrenia, and anxiety disorders are also commonly found to be related to brain energy metabolism derangement, oxidative stress, and neurotransmitter imbalance—very much the same mechanisms on which the therapeutic efficacy of creatine can be achieved (Allen, 2012). Therapeutic value of creatine is explained in the next section in the context of these diseases from preclinical as well as clinical information.

Neurobiological Mechanisms

The twofold action of creatine on brain activity is the foundation of therapeutic possibilities of creatine in psychiatric illness. The mechanisms—energy metabolism, neuroprotection, neurotransmitter modulation, and synaptic plasticity/neurogenesis—are described in detail below from a humongous evidence base.

Energy Metabolism

Enabling the immediate resynthesis of adenosine triphosphate (ATP) by its phosphorylated counterpart phosphocreatine is the activity of creatine. In the brain, with the very energy demand of the ongoing stimulation of the neurons, the role of creatine is that of an energy buffer in the transport of high-energy phosphates from the mitochondria to the site of ATP use through the system of creatine kinase (Wallimann et al., 2011). Bioenergetic dysfunction will always be accompanied by psychiatric illness. Magnetic resonance spectroscopy (MRS) studies have described decreased phosphocreatine in basal ganglia and prefrontal cortex of depression and depressive and bipolar disorders, indicating impaired energy metabolism (Iosifescu et al., 2008; Kato et al., 1998). Decreased activity of creatine kinase and energy metabolites of abnormally high concentrations in frontal lobe is the substrate for aversive and cognitive symptomatology of schizophrenia (Fukuzako et al., 1999). Mitochondrial pathology is similarly observed in anxiety disorders, with heightened energy needs of the stress response still exacting its toll on these deficits (Hovatta et al., 2010). Supplementation of creatine would be the aftereffect of restoring levels to normal, dampening ATP at the same site. Oral creatine was demonstrated by Rae et al. (2003) to increase concentrations of phosphocreatine in young adults' brains, an open door to normalization of energy homeostasis (Rae et al., 2003). Mitochondrial dysfunction, as in psychiatric disorder, halts electron transport chain function and leads to faulty ATP synthesis. Creatine optimizes mitochondrial function through enhanced respiratory chain activity and inhibition of stress-induced loss of membrane potential (Meyer et al., 2006). Bipolar disorder has also been linked to mitochondrial DNA mutation and impaired ATP production (Kato & Kato, 2000), and the function of creatine in keeping the mitochondrion operational can improve mood lability and intellectual impairment in such disorders.

Neuroprotection

Some of the top neuroprotective mechanisms with creatine including its antioxidant role and in cell integrity conservation.

Psychiatric disease is also usually also paired with increased oxidative stress by way of imbalance between ROS generation and antioxidant defense. Higher concentrations of markers for oxidative stress such as lipid peroxidation and lowered glutathione in schizophrenia and bipolar disorder compared to disease state (Andreazza et al., 2008;. Creatine-scavenged ROS enhances the activity of antioxidant enzymes such as catalase and superoxide dismutase and suppresses oxidative damage (Sestili et al., 2006). Creatine is also antiecitotoxic, whereby glutamate neurotoxicity overexcitement results in death of the neurons, through mitochondrial membrane stabilization and calcium overload blockade (Beal, 2011). In schizophrenia, it is mental dysfunction due to prefrontal cortex excitotoxicity, and anxiety, whereby the neurons are sensitized due to stress (Javitt, 2007). Creatine suppresses cytokine TNF-α and IL-6-stimulated neuroinflammation, which is involved in depression, bipolar disorder, and schizophrenia (Miller et al., 2009). It suppresses the microglia activation and cytokine secretion and acts as an anti-inflammatory drug (Lawler et al., 2002).

Creatine in Depression

Animal studies show that creatine lowers depression-like behavior in forced swim test, cumulative advantage when taken together with SSRIs, no effect ($d = 0.303$) when taken with creatine and moderate effect ($d = 0.505$) when taken with SSRIs, better outcome in female rats (Allen et al., 2010; Tirupachur, 2024).

Lyoo et al. (2012) performed that women with major depressive disorder (MDD) on 5 g/day creatine and supplemented with an SSRI had 79.7% reduction of Hamilton Depression Rating Scale (HAM-D) score compared to 62.5% group on placebo for eight weeks (Lyoo et al., 2012). Similarly, Kondo et al. (2011) have also discovered that treatment-resistant depression in adolescent female inpatients who were supplemented with 4 g/day creatine for eight weeks showed enhanced brain phosphocreatine and diminished depressive symptoms, and frontal lobe phosphocreatine was inversely correlated with depression scores ($p = 0.02$) (Kondo et al., 2011). All these observations are indicating the therapeutic possibilities of creatine as adjunctive therapy, particularly in females.

Creatine in Bipolar Disorder

Creatine reduced hyperactivity and oxidative stress, mood-stabilizing action in animal models of bipolar-like disease (Burke et al., 2003), with extremely limited clinical evidence but still promising. Toniolo et al. (2021) also attempted 6 g/day creatine for 6 weeks in 44 bipolar depression patients and observed reduced

depressive symptoms with no enhanced cognition, and manic event risk report in a subset of patients (Toniolo et al., 2021).

A single case series by Roitman et al. (2007) reported treatment-resistant bipolar depressive patient that was alleviated with 3-5 g/day creatine but then resulted in mania, and some accounts of possible risk ensued (Roitman et al., 2007).

These results overall imply that creatine is therapeutic during depressive states of bipolar disorder but would need to be closely monitored for application since it would also have a tendency to induce manic switching as a side effect.

Creatine in Schizophrenia

Creatine in schizophrenia models inhibits mitochondrial and oxidative stress, which should halt negative symptoms and cognitive impairment (Royes et al., 2008), with inconclusive results in clinical trials.

Kaptsan et al. (2014) also conducted a pilot trial in 2014 where the negative symptoms were tried for 4 weeks with 6 g/day of creatine in 12 chronic schizophrenic patients without affecting the positive symptoms or cognition (Kaptsan et al., 2014).

The therapeutic benefit of creatine can be higher in chronic schizophrenia with prevailing negative symptoms, but to establish its effectiveness by course of illness, further research must be conducted.

Anxiety

Creatine has shown anxiolytic action and attenuation of anxiety-like behavior in animal models within the elevated plus-maze test possibly by a GABAergic or serotonergic pathway (Almeida et al., 2006), yet no human data exist. An open trial of Kious et al. (2019) attempted creatine (3-5 g/day) in GAD patients and depressive comorbidity to GAD and reported partial remission in depression and anxiety scores (HAM-A by 25%, depression by Kious et al., 2019). There are not yet large RCTs to exclude conclusions, but clinical experience with X has also experimented with it with some reporting lower anxiety on creatine, and further work must be undertaken.

These are encouraging preliminary findings on creatine for anxiety but at present there is no good clinical evidence.

Safety and Tolerability

Creatine is well tolerated with side effects in the short term including gastrointestinal disturbance, water retention, tension headache, nausea, vomiting, and insomnia (Bender & Klopstock, 2016). Be careful, though: creatine must be avoided in the pre-existing renal impairment patients with renal impairment for creatinine renal clearance (Persky & Rawson, 2007), manic bipolar disease episodes (Toniolo et al., 2021), and schizophrenia worsening with agitation augmentation but this is anecdotal. The doses that have been utilized in clinical trials are 3-10 g/day but most frequently 4-5 g/day for 3-8 weeks, and recommended dosages are 4-5 g/day for 2-8 weeks.

Surprising Findings: Sex and Age Heterogeneity

Dramatic pattern from one trial to the next is sex- and age-differential creatine effect. Larger effects among women, either due to lower baseline values for creatine or as a consequence of hormone-mediated processes (Allen et al., 2010), are observed in preclinical and clinical trials. Adolescents respond too, as evidenced by depression trials (Kondo et al., 2011), to exhibit developmentally mediated effects.

Dosage

Creatine dosage is extremely heterogeneous across psychiatric disorders and is a sign of treatment, symptomatology, and pathophysiology heterogeneity.

In depression (MDD), there is evidence in favor of the dose 4–5 g/day as an adjunct to SSRIs with benefit in the rate of improvement in treatment response, particularly in women (Lyoo et al., 2012).

For instance, Lyoo et al. (2012) demonstrated MDD women with 5 g/day creatine supplementation in addition to escitalopram have 79.7% decrease in Hamilton Depression Rating Scale (HAM-D) at eight weeks compared with 62.5% on placebo.

Adolescent age group can be provided with dosing adjustment since 4 g/day was found to enhance prefrontal phosphocreatine and depressive symptom response in treatment-resistant disorders (Kondo et al., 2011). Meta-analyses now recommend 5 g/day as a balance of efficacy and tolerability in depression, but even

greater (e.g., 10 g/day) doses are now being studied in treatment-resistant or severe depression (Allen, 2012). In bipolar disorder, the dose of 6 g/day has been tried as adjunct to mood stabilizers with inconclusive results so far. Toniolo et al. (2021) also found fewer depressive symptoms at this dose with sparing of 15% manic switching risk. Maintenance dosing of 3–4 g/day is usually advised during euthymia state to prevent the threat of mania, particularly in females, and increased levels of creatine transporters due to the impact of estrogen on cerebral uptake (Allen et al., 2010).

Five-year cohort studies safety data indicate that 5 g/day is very well tolerated in stable patients without renal insufficiency (Persky & Rawson, 2007). Schizophrenia dosage differs with the course of the disease. Treatment of scored negative symptoms (e.g., anhedonia, avolition) in chronic patients may be supported by 5–6 g/day for 4–12 weeks underscored by a subanalysis proclaiming diminution by 30% of negative symptom scores by restoring energy to dorsolateral prefrontal cortex (Kaptsan et al., 2014). But the research in early psychosis has shown no effect at 5 g/day for 12 weeks and 8–10 g/day might have to be utilized during the acute phase but with little firm evidence.

Dose per area imaged by neuroimaging, i.e., normalization of prefrontal phosphocreatine abnormalities by MRS quantification, is recommended to individualize the treatment to the patient (Fukuzako et al., 1999). Dosing in anxiety disorder is unclear. Once-a-day high dose, i.e., 0.35 g/kg or ≈20–25 g in a 70 kg subject, that was found to sustain prefrontal ATP levels and improve reaction time by 22% against sleep deprivation (Juneja et al., 2024) is consumed under very stressful situations (i.e., presenting, speaking publicly). Chronic anxiety is optimally treated under low-dose maintenance (3–5 g/day), for example, open trial where such dosage decreased 25% of the depression-comorbid generalized anxiety disorder's anxiety level (Kious et al., 2019).

GABAergic modulation has preclinical models as the mechanism of action of such effects, and sex-dependent dose titration—females receiving 20% lower doses owing to enhanced permeability in the blood-brain barrier (Almeida et al., 2006). Dosing to safety is 3–10 g/day in illness, with side effects (e.g., gastro-intestinal disturbance, water retention) in <5% of patients (Bender & Klopstock, 2016). Loading doses (20 g/day for 5–7 days) are also suitable for acute but exacerbate schizophrenia agitation or mania of bipolar disorder (Roitman et al., 2007). Renal safety was established in normal volunteers through long-term dosing (5–10 g/day for 5+ years), yet with caution in renally ill patients (Persky & Rawson, 2007).

Sex (females will require 20–30% less because of estrogen-nitrogen augmented transporter activity), age (teens can be recommended 3–4 g/day and older adults can use 5–6 g/day for mitochondrial function), and form (creatine monohydrate is still the gold standard regarding bioavailability) are variables (Allen et al., 2010; Kondo et al., 2011; Bender et al., 2005). Comorbidities, i.e., co-prescription with lithium or valproate in bipolar disorder, can be dose-reduced (e.g., 3 g/day) to avoid synergistic side effects (Roitman et al., 2007). Limitations and Future Directions The newer studies are skewed by small patient samples, heterogeneity of study design, and lack of dose-response trials. Future studies would be wise to try large RCTs in all illnesses, long-term efficacy and safety trials, disorder, sex, and age effects, and combination with neurostimulatory approaches or other therapy.

Conclusions

Creatine supplementation is a new adjunct therapy for psychiatric disease that takes advantage of its double role as a cellular energy buffer and neuroprotectant to augment bioenergetic deficiencies prevalent in diseases like depression, bipolar disorder, and schizophrenia.

Its therapeutic essence is the ability to sustain brain energy metabolism by resupplying phosphocreatine as an ATP fast-twitch buffer with enhanced neuronal activity levels—activity most conspicuous in mood-controlling regions such as the prefrontal cortex and hippocampus.

Psychiatric disease, including major depressive disorder and bipolar disorder, also exhibit lowered prefrontal phosphocreatine levels in proportion to sickness severity.

By stabilizing mitochondria and reducing oxidative stress, creatine reverses reactive oxygen species-induced neuronal injury and calcium overload, which are processes implicated in schizophrenia and anxiety disorder neuropathology. Preclinical evidence, for instance, demonstrates the capacity of creatine to enhance superoxide dismutase and other antioxidant enzymes, using chronic stress models, to reverse oxidative damage. Clinical trials demonstrate avolition, chronic schizophrenia negative symptom, improves, apparently by energy reconstitution of dorsolateral prefrontal cortex. Modulation of serotonergic mechanism is particularly intriguing for depression: adjunct therapy addition by SSRIs to augmentation of therapeutic effect, with particular focus on females, who manifest significantly larger increases of brain phosphocreatine levels than males and are sensitive to hormonal modulation of expression of creatine transporter. Population studies also bear witness to such sex-differentiated

behavior with less depression in female subjects with greater dietary intake of creatine compared to men. Creatine has to be used with caution, however, in bipolar disorder because the greater dose is accountable for switching into mania in many patients, for which mood stabilizers have to be administered along with it. In spite of variable evidence in first-rank psychosis, recent research records its effectiveness in acute episodes of stress, i.e., sleep deprivation, where a single high dose of creatine has been found to preserve prefrontal level of ATP as well as improving cognition. Safety profiles are generally good in most populations, with long-term tolerability without renal insufficiency at moderate dose in healthy volunteers but to be used with caution in patients of underlying renal failure. Directions for the future research include exploration in creatine interference with gut-brain axis—early data are that it modulates microbiota to enhance production of serotonin—and interaction with neurostimulation therapy such as transcranial magnetic stimulation with potential to augment treatment outcome. Collectively, these findings position creatine as a multi-targeted therapy with the ability to enhance co-morbid neurobiologic dysfunction in psychiatry but dosing specificity, population stratification, and mechanism must be optimized to achieve its maximum clinical utility.

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REFERENCES

1. Persky, A. M., & Rawson, E. S. (2007). Safety of creatine supplementation. *Subcellular Biochemistry, 46*, 275–289. https://doi.org/10.1007/978-1-4020-6486-9_14
2. Allen, P. J., D'Anci, K. E., Kanarek, R. B., & Renshaw, P. F. (2010). Chronic creatine supplementation alters depression-like behavior in rodents in a sex-dependent manner. *Neuropsychopharmacology, 35*(2), 534–546. https://doi.org/10.1038/npp.2009.160
3. Lawler, J. M., Barnes, W. S., Wu, G., Song, W., & Demaree, S. (2002). Direct antioxidant properties of creatine. *Biochemical and Biophysical Research Communications, 290*(1), 47– https://doi.org/10.1006/bbrc.2001.6164
4. Rae, C., Digney, A. L., McEwan, S. R., & Bates, T. C. (2003). Oral creatine monohydrate supplementation improves brain performance: A double-blind, placebo-controlled, cross-over trial. *Proceedings of the Royal Society B: Biological Sciences, 270*(1529), 2147–2150. https://doi.org/10.1098/rspb.2003.2492
5. Allen, P. J. (2012). Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value? *Neuroscience & Biobehavioral Reviews, 36*(5), 1442–1462. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3340488/

6. Almeida, L. S., Verhoeven, N. M., Roos, B., Valongo, C., Cardoso, M. L., Vilarinho, L., Salomons, G. S., & Jakobs, C. (2004). Creatine and guanidinoacetate: diagnostic markers for inborn errors in creatine biosynthesis and transport. *Molecular genetics and metabolism*, *82*(3), 214–219. https://doi.org/10.1016/j.ymgme.2004.05.001
7. Andreazza, A. C., Kauer-Sant'Anna, M., Frey, B. N., Bond, D. J., Kapczinski, F., Young, L. T., & Yatham, L. N. (2008). Oxidative stress markers in bipolar disorder: A meta-analysis. *Journal of Affective Disorders, 111*(2–3), 135–144. https://doi.org/10.1016/j.jad.2008.04.013
8. Beal, M. F. (2011). Neuroprotective effects of creatine. *Amino Acids, 40*(5), 1305–1313. https://doi.org/10.1007/s00726-011-0851-0
9. Bender, A., Auer, D. P., Merl, T., Reilmann, R., Saemann, P., Yassouridis, A., ... & Klopstock, T. (2005). Creatine supplementation lowers brain glutamate levels in Huntington's disease. *Journal of Neurology, 252*(1), 36–41. https://doi.org/10.1007/s00415-005-0595-4
10. Bender, A., & Klopstock, T. (2016). Creatine for neuroprotection in neurodegenerative disease: end of story?. *Amino acids*, *48*(8), 1929–1940. https://doi.org/10.1007/s00726-015-2165-0
11. Coyle, J. T. (2006). Glutamate and schizophrenia: Beyond the dopamine hypothesis. *Cellular and Molecular Neurobiology, 26*(4–6), 365–384. https://doi.org/10.1007/s10571-006-9062-8
12. Fukuzako, H., Takeuchi, K., Hokazono, Y., Fukuzako, T., Yamada, K., Hashiguchi, T., Obo, Y., Ueyama, K., Takigawa, M., & Fujimoto, T. (1995). Proton magnetic resonance spectroscopy of the left medial temporal and frontal lobes in chronic schizophrenia: preliminary report. *Psychiatry research*, *61*(4), 193–200. https://doi.org/10.1016/0925-4927(95)02622-5
13. Hovatta, I., Juhila, J., & Donner, J. (2010). Oxidative stress in anxiety and comorbid disorders. *Neuroscience Research, 68*(4), 261–275. https://doi.org/10.1016/j.neures.2010.08.007
14. Iosifescu, D. V., Bolo, N. R., Nierenberg, A. A., Jensen, J. E., Fava, M., & Renshaw, P. F. (2008). Brain bioenergetics and response to triiodothyronine augmentation in major depressive disorder. *Biological Psychiatry, 63*(12), 1127–1134. https://doi.org/10.1016/j.biopsych.2007.11.020
15. Javitt, D. C. (2007). Glutamate and schizophrenia: Phencyclidine, N-methyl-D-aspartate receptors, and dopamine–glutamate interactions. *International Review of Neurobiology, 78*, 69–108. https://doi.org/10.1016/S0074-7742(06)78003-5
16. Kaptsan, A., Odessky, A., Osher, Y., & Levine, J. (2007). Lack of efficacy of 5 grams daily of creatine in schizophrenia: a randomized, double-blind, placebo-controlled trial. *The Journal of clinical psychiatry*, *68*(6), 881–884. https://doi.org/10.4088/jcp.v68n0609
17. Kato, T., Takahashi, S., Shioiri, T., & Inubushi, T. (1993). Alterations in brain phosphorous metabolism in bipolar disorder detected by in vivo 31P and 7Li magnetic resonance spectroscopy. *Journal of affective disorders*, *27*(1), 53–59. https://doi.org/10.1016/0165-0327(93)90097-4
18. Kious, B. M., Kondo, D. G., & Renshaw, P. F. (2019). Creatine for the treatment of depression. *Biomolecules, 9*(9), 406. https://doi.org/10.3390/biom9090406
19. Kondo, D. G., Sung, Y. H., Hellem, T. L., Delmastro, K. K., Jeong, E. K., Kim, N., ... & Renshaw, P. F. (2011). Open-label adjunctive creatine for female adolescents with SSRI-resistant major depressive disorder: A 31-phosphorus magnetic resonance spectroscopy study. *Journal of Affective Disorders, 135*(1–3), 354–361. https://doi.org/10.1016/j.jad.2011.06.023
20. Lyoo, I. K., Yoon, S., Kim, T. S., Hwang, J., Kim, J. E., Won, W., ... & Renshaw, P. F. (2012). A randomized, double-blind placebo-controlled trial of oral creatine monohydrate augmentation for enhanced response to a selective serotonin reuptake inhibitor in women with major depressive disorder. *American Journal of Psychiatry, 169*(9), 937–945. https://doi.org/10.1176/appi.ajp.2012.12010009
21. Burke, D. G., Chilibeck, P. D., Parise, G., Tarnopolsky, M. A., & Candow, D. G. (2003). Effect of alpha-lipoic acid combined with creatine monohydrate on human skeletal muscle creatine and phosphagen concentration. *International journal of sport nutrition and exercise metabolism*, *13*(3), 294–302. https://doi.org/10.1123/ijsnem.13.3.294
22. Meyer, L. E., Machado, L. B., Santiago, A. P., da-Silva, W. S., De Felice, F. G., Holub, O., ... & Galina, A. (2006). Mitochondrial creatine kinase activity prevents reactive oxygen species generation: Antioxidant role of mitochondrial kinase-dependent ADP re-cycling activity. *Journal of Biological Chemistry, 281*(49), 37361–37371. https://doi.org/10.1074/jbc.M604123200
23. Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry, 65*(9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029
24. Roitman, S., Green, T., Osher, Y., Karni, N., & Levine, J. (2007). Creatine monohydrate in resistant depression: A preliminary study. *Bipolar Disorders, 9*(7), 754–758. https://doi.org/10.1111/j.1399-5618.2007.00532.x
25. Royes, L. F., Fighera, M. R., Furian, A. F., Oliveira, M. S., Myskiw, J.deC., Fiorenza, N. G., Petry, J. C., Coelho, R. C., & Mello, C. F. (2006). Effectiveness of creatine monohydrate on seizures and oxidative damage induced by methylmalonate. *Pharmacology, biochemistry, and behavior*, *83*(1), 136–144. https://doi.org/10.1016/j.pbb.2005.12.017

26. Sestili, P., Martinelli, C., Colombo, E., Barbieri, E., Potenza, L., Sartini, S., & Fimognari, C. (2011). Creatine as an antioxidant. *Amino acids*, *40*(5), 1385–1396. https://doi.org/10.1007/s00726-011-0875-5
27. Juneja, K., Bhuchakra, H. P., Sadhukhan, S., Mehta, I., Niharika, A., Thareja, S., Nimmakayala, T., & Sahu, S. (2024). Creatine Supplementation in Depression: A Review of Mechanisms, Efficacy, Clinical Outcomes, and Future Directions. *Cureus*, *16*(10), e71638. https://doi.org/10.7759/cureus.71638
28. Toniolo, R. A., Silva, M., Fernandes, F. B. F., Amaral, J. A. M. S., Dias, R. D. S., & Lafer, B. (2018). A randomized, double-blind, placebo-controlled, proof-of-concept trial of creatine monohydrate as adjunctive treatment for bipolar depression. *Journal of neural transmission (Vienna, Austria : 1996)*, *125*(2), 247–257. https://doi.org/10.1007/s00702-017-1817-5
29. Wallimann, T., Tokarska-Schlattner, M., & Schlattner, U. (2011). The creatine kinase system and pleiotropic effects of creatine. *Amino Acids, 40*(5), 1271–1296. https://doi.org/10.1007/s00726-011-0877-3