International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	THE ROLE OF CREATINE IN NEUROLOGICAL DISORDERS: A LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3722
RECEIVED	15 July 2025
ACCEPTED	14 September 2025
PUBLISHED	30 September 2025
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THE ROLE OF CREATINE IN NEUROLOGICAL DISORDERS: A LITERATURE REVIEW

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ABSTRACT

Creatine, widely known as a performance-enhancing supplement for athletes and bodybuilders is increasingly recognized for its potential neuroprotective properties. Beyond its well-established role in energy metabolism and muscle physiology, creatine appears to influence brain function by supporting ATP homeostasis, reducing oxidative stress, and stabilizing neuronal membranes. Recent studies have suggested that creatine supplementation may benefit individuals with neurodegenerative disorders such as Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS) and Alzheimer's disease. Additionally, preliminary findings indicate a potential role for creatine in mitigating the effects of acute brain injuries and mood disorders, including major depressive disorder. Despite promising experimental data, the clinical efficacy of creatine in neurological settings remains under investigation, with inconsistent results across human trials. This review aims to summarize current knowledge on the neuroprotective effects of creatine and critically assess the quality of available evidence.

KEYWORDS

Creatine, Neuroprotection, Brain Energy Metabolism, Neurodegenerative Diseases, Parkinson's Disease, Alzheimer's Disease, Huntington's Disease, Amyotrophic Lateral Sclerosis, Depression, Traumatic Brain Injury

CITATION

Amin Omidi, Maja Ćwiek, Klaudia Malec, Bartosz Krawiec, Bartłomiej Zarębski, Olaf Jadanowski, Jakub Sójka, Maksymilian Szombara, Michał Mokrzyński, Piotr Szyszka. (2025) The Role of Creatine in Neurological Disorders: A Literature Review. *International Journal of Innovative Technologies in Social Science.* 3(47). doi: 10.31435/ijitss.3(47).2025.3722

Introduction

Creatine (N-(aminoiminomethyl)-N-methyl glycine) is a nitrogen-rich compound that occurs naturally in the body and plays a key role in maintaining cellular energy balance. Although often described as an amino acid, creatine is a derivative formed from the amino acids arginine and glycine through the action of the enzyme L-arginine:glycine amidinotransferase (AGAT), which produces guanidinoacetate (GAA). This intermediate is then methylated by guanidinoacetate N-methyltransferase (GAMT), using S-adenosyl methionine (SAMe) as a methyl donor, to generate creatine AGAT is expressed in organs such as the kidneys, liver, pancreas, and certain brain regions. The majority of GAA is synthesized in the kidneys and subsequently converted into creatine in the liver.[1] The primary function of creatine within the cell is to form phosphocreatine (PCr) by binding with inorganic phosphate (Pi), thereby acting as a rapid reserve of high-energy phosphate groups that facilitates the regeneration of adenosine triphosphate (ATP) from adenosine diphosphate (ADP) and Pi, supporting cellular energy demands during metabolic activity.[2] Approximately 95% of the body's total creatine content is localized in skeletal muscle, while smaller proportions are distributed across other tissues such as the heart, brain, and testes. Of this muscular creatine pool, nearly two-thirds exists in the form of phosphocreatine (PCr), with the remaining one-third present as unbound, free creatine (Cr).[3] Approximately 1–2% of the creatine stored in muscle tissue undergoes non-enzymatic degradation each day, resulting in the formation of creatinine, a metabolic byproduct that is subsequently eliminated from the body via urinary excretion.[4] In recent years, creatine has gained significant scientific interest beyond its well-established role in muscle metabolism, particularly regarding its involvement in the central nervous system. Studies have begun to explore its potential neuroprotective properties, examining how creatine may support neuronal energy homeostasis, reduce oxidative stress, and improve mitochondrial function. As a result, creatine is being investigated as a therapeutic candidate in a range of neurological disorders, including neurodegenerative diseases or traumatic brain injuries.

Methodology

This review was conducted using a systematic approach to identify and analyze relevant scientific literature on the potential neuroprotective effects of creatine. We searched **PubMed** and **Google Scholar** databases. Articles were searched using following words : *"creatine", "neuroprotection", "brain energy metabolism", "* neurodegenerative diseases", *"Parkinson's disease", "Alzheimer's disease", "Huntington's disease", "*amyotrophic lateral sclerosis*", "depression", "traumatic brain injury"*.

Results

Mechanisms of creatine action in the nervous system

Creatine is commonly associated with muscle energy metabolism, but recent studies have shown its broader potential in supporting brain function. Within the central nervous system, creatine plays an essential role in maintaining energy homeostasis, particularly under conditions of metabolic stress such as hypoxia, oxidative damage, or neurodegenerative processes. In neurons, creatine is enzymatically converted into phosphocreatine (PCr), which serves as a rapidly accessible energy buffer. This system allows for the immediate regeneration of ATP from ADP during moments of high energy demand, helping to preserve critical neuronal functions such as membrane potential maintenance, neurotransmitter release, and ion balance.[5]

The creatine–PCr shuttle becomes especially relevant in cells with high metabolic rates such as glutamatergic neurons, which are particularly sensitive to energy fluctuations. In pathological states like ischemia or neurodegenerative diseases, the availability of creatine may delay the onset of energetic failure, potentially preventing irreversible neuronal damage.[5] Beyond energy buffering, creatine has demonstrated antioxidant effects. It can directly scavenge reactive oxygen species and indirectly support cellular redox balance by maintaining mitochondrial efficiency. This contributes to reduced oxidative stress and improved neuronal survival.[6]

Furthermore, creatine stabilizes cellular membranes, protecting them from structural damage and preventing pathological ion fluxes that often occur in stressed or injured cells.[6] It also appears to play a regulatory role in glutamatergic neurotransmission. Excess extracellular glutamate is a well-known contributor to excitotoxicity, a mechanism of neuronal death observed in both acute brain injury and chronic neurological disorders. By supporting ATP-dependent glutamate clearance and maintaining mitochondrial integrity, creatine may reduce excitotoxic damage and improve overall neuronal resilience.[7]

In terms of cognitive functions results are mixed. Studies have shown benefits of creatine supplementation in certain populations, such as vegetarians and the elderly.[8-9] However, in young, healthy adults, creatine supplementation has not been found to improve cognitive performance.[10] **There was also no consensus among studies regarding its effects on memory functions.** In a head-to-head comparison between vegetarians and omnivores, there was observed that creatine supplementation (20 g/day for 5 days) led to greater improvements in memory performance among vegetarians compared to those who consume meat.[11] However, other studies have not demonstrated any positive impact of creatine on memory-related outcomes in adults.[12]

Creatine in Neurodegenerative diseases

In recent years, creatine has gained attention as a potential supportive agent in the management of various neurodegenerative diseases. These disorders, including Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease, are characterized by progressive neuronal loss, impaired energy metabolism, and mitochondrial dysfunction—areas where creatine's mechanisms of action may offer some benefit. This section will explore the effects of creatine in these neurological disorders.

Creatine for Parkinson's disease

Parkinson's disease ranks among the most prevalent neurodegenerative disorders and is clinically defined by symptoms like muscle rigidity or resting tremor and is linked to a dopamine deficit in the substantia nigra region of the brain. Additionally, factors like mitochondrial dysfunction, increased oxidative stress, and abnormal protein processing are believed to significantly contribute to the disease's underlying pathophysiology.[13] Given creatine's ability to support cellular energy metabolism, buffer ATP levels, and mitigate oxidative stress, it has been proposed as a potential neuroprotective agent in Parkinson's disease.

In the most comprehensive and recent large-scale study examining creatine supplementation 1,741 participants with early-stage Parkinson's disease were assigned to receive either creatine monohydrate at a dose of 10 grams per day or a placebo. The study was discontinued ahead of schedule because interim results

indicated that creatine supplementation had no meaningful effect on slowing the progression of Parkinson's disease compared to placebo. These outcomes imply that, at the administered dose, creatine alone does not offer therapeutic benefit in modifying the course of the disease.[14]

A randomized controlled trial conducted in 2015 examined the effects of a combined supplementation regimen involving creatine and coenzyme Q10 (CoQ10) in individuals diagnosed with Parkinson's disease and mild cognitive impairment (PD-MCI). Participants were administered 5 grams of creatine monohydrate twice daily along with 100 mg of CoQ10 three times per day over a period of 18 months. The study demonstrated that this combination therapy significantly reduced the rate of cognitive decline when compared to a placebo group, as assessed by the Montreal Cognitive Assessment (MoCA). Additionally, individuals receiving the supplements showed lower levels of plasma phospholipids, which may point toward underlying neuroprotective effects. These results suggest that although creatine alone may not yield measurable benefits in modifying the course of Parkinson's disease, its synergistic use with CoQ10 could support cognitive function in patients experiencing early cognitive impairment.[15]

Despite these findings, current evidence does not support the use of creatine monotherapy as an effective treatment for PD. Further research is needed to explore the potential benefits of creatine in combination with other therapeutic agents.

Creatine for Alzheimer's disease

Alzheimer's disease (AD) is the most prevalent type of dementia, marked by progressive deterioration in memory, cognitive function, and the ability to perform daily activities. On a cellular level, the disease is associated with mitochondrial dysfunction, impaired cerebral glucose metabolism, sustained oxidative stress, and synaptic loss — all of which represent potential mechanisms through which creatine could exert beneficial effects.[16]

A 2020 study, McMorris et al. explored the effects of six weeks of creatine supplementation on cognitive function in a rat model of inflammation-induced cognitive impairment. The findings showed that creatine reduced the memory deficits caused by lipopolysaccharide (LPS)-induced neuroinflammation, suggesting a potential neuroprotective role. These results indicate that creatine may be a promising therapeutic candidate for addressing cognitive decline related to inflammatory processes, such as those observed in mild cognitive impairment (MCI).[17]

Another recent study explored the impact of creatine supplementation on behavioral outcomes, molecular markers, and mitochondrial function in 3xTg mice, a widely used transgenic model of Alzheimer's disease. The analysis focused on the hippocampus, a brain region particularly vulnerable to AD-related damage. The results revealed sex-specific effects: spatial memory improvements and increased expression of synaptic plasticity-related proteins were observed exclusively in female mice. Interestingly, enhanced mitochondrial bioenergetics were noted in both sexes. These findings suggest that creatine may offer greater cognitive benefits for females at risk of developing Alzheimer's disease, although further studies are needed to confirm its long-term efficacy and evaluate its relevance for male populations.[18]

A clinical trial known as CABA is currently in progress to investigate the safety and potential benefits of high-dose creatine supplementation (20 g per day over eight weeks) in individuals with Alzheimer's disease. The primary focus of the study is to examine whether creatine alters brain creatine concentrations, improves cognitive function, and enhances mitochondrial activity.[19]

Creatine appears to hold therapeutic potential as an adjunctive intervention in the management of Alzheimer's disease, especially during its early phases. Nonetheless, additional clinical studies are required to validate its efficacy and to determine appropriate dosing regimens and treatment duration.

Creatine for Huntington's disease

Huntington's disease (HD) is an autosomal dominant neurodegenerative condition marked by a gradual worsening of motor function, cognitive abilities, and psychiatric health. Currently, there are no approved treatments that effectively slow the progression of clinical symptoms. The disease is driven by the mutant huntingtin protein (mtHtt), which initiates a range of molecular disturbances—among them disrupted cellular energy metabolism, a pathway that has been explored as a potential target for therapeutic intervention.[20]

Initial studies in animal models of Huntington's disease demonstrated that creatine supplementation was able to postpone symptom development, protect against neuronal degeneration, and enhance motor performance in mice.[21-22]

A 2006 Phase II trial found that creatine was safe and well-tolerated in patients with early-stage HD.[23] However the 2017 CREST-E trial remains the most up-to-date and extensive clinical investigation into creatine use for Huntington's disease. In this placebo-controlled study, over 550 early-stage HD patients were given up to 40 grams of creatine per day to evaluate whether it could slow functional deterioration. The trial was halted prematurely due to interim results showing no therapeutic benefit. Participants receiving creatine actually showed a slightly faster decline in functional abilities compared to the placebo group, and gastrointestinal side effects were more frequently reported. Despite promising preclinical data, this high-dose creatine supplementation did not produce meaningful clinical improvements in patients with HD. [24]

Creatine for Amyotrophic lateral sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a complex neurodegenerative disorder marked by the progressive loss of both upper motor neurons—extending from the cerebral cortex to the brainstem and spinal cord—and lower motor neurons, which connect the brainstem or spinal cord to muscles. This widespread neuronal degeneration results in a combination of motor dysfunction and non-motor symptoms.[25] Several hypotheses propose that factors such as infections, glutamate-induced excitotoxicity, oxidative damage, neuroinflammation, protein misfolding, mitochondrial impairment, and disruptions in cytoskeletal structure may all contribute to the disease process.[26]

In animal models of ALS, creatine supplementation produced encouraging outcomes, including extended survival and preservation of motor function.[27]

In 2004 clinical studies involving ALS patients, creatine supplementation was well tolerated but did not lead to any measurable improvement across assessed outcomes. Confidence interval analysis indicated that, although the study was designed to detect a 50% or greater reduction in the rate of muscle strength decline, even a 23% effect size appeared unlikely. Additionally, the study confirmed that motor unit number estimation (MUNE) was both reproducible and well tolerated, suggesting its potential utility as a reliable outcome measure in future ALS trials. [28]

A 2012 Cochrane meta-analysis, which reviewed three clinical trials involving a total of 386 participants, found no statistically significant effect of creatine supplementation on survival or disease progression in ALS patients. However, the supplement was generally well tolerated across studies.[29]

Currently, no active clinical trials are investigating creatine as a treatment for ALS. Although previous studies have not demonstrated significant therapeutic benefits, creatine continues to be of scientific interest due to its bioenergetic and neuroprotective properties.

Creatine and depression

In recent years, growing attention has been directed toward the relationship between cerebral energy metabolism and mental health, particularly in the context of mood disorders like depression. Major depressive disorder (MDD) is expected to become the foremost contributor to the global burden of disease by the year 2030.[30]

Animal research has shown that creatine may help alleviate depressive symptoms by acting on several biological systems—most notably by influencing serotonin levels, activating adenosine receptors, and promoting brain cell growth and adaptability.[31-35]

Kondo et al. investigated how creatine affects brain energy metabolism in adolescents with depression unresponsive to SSRIs, using phosphorus-31 magnetic resonance spectroscopy. They found that higher levels of phosphocreatine in the brain were associated with improved mood.[36]

Toniolo et al. studied creatine's potential as an adjunct therapy by administering a higher dose of 6 grams per day over a six-week period in patients diagnosed with bipolar depression. The study found a significant reduction in depressive symptoms following supplementation, suggesting that creatine may offer therapeutic benefits in bipolar depression.[37]

An open-label pilot study explored the effects of combining creatine monohydrate and 5-hydroxytryptophan (5-HTP) as an add-on therapy for women with major depressive disorder who had not responded adequately to treatment with SSRIs or SNRIs. Participants received a daily dose of 5 grams of creatine and 100 mg of 5-HTP twice daily over an 8-week period.

By the end of the intervention, participants showed a significant reduction in depressive symptoms—approximately 60%—as measured by the Hamilton Depression Rating Scale, and no serious adverse events were reported.

These preliminary findings point to the potential of creatine and 5-HTP as a combined therapeutic strategy for treatment-resistant depression in women. Nonetheless, due to the study's limited sample size and open-label design, further randomized, placebo-controlled trials are necessary to confirm the efficacy and safety of this approach.[38]

Another studies have also explored creatine's biochemical and neuroimaging characteristics, revealing changes in brain energy metabolism and neurotransmitter activity that could help explain its potential antidepressant properties.[39-41]

While further studies—particularly those with larger cohorts and extended follow-up periods—are necessary, existing data suggest that creatine may serve as a promising add-on therapy for depression, especially in patients with metabolic impairments or inadequate response to conventional antidepressants.

Creatine for traumatic brain injury (TBI)

A growing body of evidence indicates that creatine not only enhances cognitive performance under stress but may also offer direct neuroprotective effects following traumatic brain injury. One key observation is the post-injury depletion of brain creatine stores. [42-44] Animal studies have shown that pre-injury creatine supplementation can substantially reduce the severity of brain damage—by up to half in some models.[45]

Creatine supplementation shows neuroprotective potential both before and after mild traumatic brain injury (mTBI). Studies suggest that pre-injury supplementation can reduce cellular damage and metabolic disruption, while post-injury use may alleviate symptoms and improve recovery. However, research specifically examining creatine use following mTBI remains limited.[46]

Clinical evidence on the effectiveness of creatine supplementation in humans after severe traumatic brain injury (TBI) is limited to a single pilot study involving children and adolescents (aged 1–18 years) with severe TBI (Glasgow Coma Scale scores between 3 and 9). [47-49] This open-label randomized study found that daily supplementation with 0.4 g/kg of creatine, administered orally or via nasogastric tube, was associated with shorter durations of post-traumatic amnesia, intubation, and hospitalization. Participants also showed improvements in neurological function, cognition, behavior, social interaction, and self-care within 3 to 6 months of treatment. [47] Follow-up reports from the same patient group noted additional benefits, including reduced incidence of headaches, dizziness, fatigue [48], improved speech and language comprehension.[49]

In the context of post-traumatic epilepsy (PTE), findings from animal studies are mixed. Some research in rat models has shown that creatine supplementation, initiated one week after TBI, can delay the onset of myoclonic and tonic-clonic seizures, reduce seizure duration and intensity, and offer continued neuroprotection even after supplementation is stopped. Creatine also appears to protect hippocampal neurons and preserve GABAergic signaling, which is critical, as long-term damage following TBI is often driven by excitotoxicity.[50]

However, other studies have reported less favorable outcomes. While creatine reduced oxidative stress markers such as protein carbonylation and lipid peroxidation, it did not reverse reductions in Na^+/K^+-ATPase activity. In some cases, creatine supplementation even led to shorter latency before seizures and prolonged seizure episodes.[51]

Although current results are promising, creatine still isn't part of routine clinical treatment for TBI. More extensive and better-designed studies are needed to figure out the right dose, timing, and how long the supplementation should last. Still, because it's safe, affordable, and has a solid biological rationale, creatine is seen as a potentially useful supportive option—especially in the early stages after injury.

Discussion

Although creatine is most widely known for its role in supporting muscle function, an increasing number of studies point to its potential benefits in the nervous system. This review has explored recent evidence on its application in neurological and neuropsychiatric conditions. In animal studies, creatine has repeatedly demonstrated neuroprotective effects, such as enhancing cellular energy production, stabilizing mitochondrial function, and lowering oxidative stress. These actions may be particularly beneficial in diseases like Parkinson's, Huntington's, Alzheimer's, ALS, depression, and traumatic brain injury.

However, despite encouraging results from preclinical models, outcomes from human clinical trials have been inconsistent. For example, in Huntington's disease and ALS, creatine was generally safe and well tolerated but failed to significantly alter disease progression in larger trials. On the other hand, studies involving patients with depression or traumatic brain injury showed more promising results, especially when creatine was combined with standard therapies. These differences may be due to factors such as inconsistent study designs, varying treatment durations, disease stages at enrollment, or differences in the types and doses of creatine used.

Conclusions

Creatine is a well-tolerated, accessible, and biologically active compound with growing evidence supporting its potential in neurological health. While its clinical effectiveness remains uncertain in several areas, preclinical findings and selected human studies suggest that it may play a valuable role as a supportive therapy, particularly when introduced early or used in combination with standard treatments. Further well-designed clinical trials are needed to establish its efficacy, determine optimal treatment parameters, and identify target populations.

REFERENCES

1. Kreider, R. B., Jäger, R., & Purpura, M. (2022). Bioavailability, efficacy, safety, and regulatory status of creatine and related compounds: A critical review. *Nutrients, 14*(5), 1035. https://doi.org/10.3390/nu14051035
2. Kreider, R. B., & Stout, J. R. (2021). Creatine in health and disease. *Nutrients, 13*(2), 447. https://doi.org/10.3390/nu13020447
3. Kreider, R., & Jung, Y. (2011). Creatine supplementation in exercise, sport, and medicine. *Journal of Exercise Nutrition and Biochemistry, 15*(2), 53–69. https://doi.org/10.5717/jenb.2011.15.2.53
4. Hultman, E., Söderlund, K., Timmons, J. A., Cederblad, G., & Greenhaff, P. L. (1996). Muscle creatine loading in men. *Journal of Applied Physiology, 81*(1), 232–237. https://doi.org/10.1152/jappl.1996.81.1.232
5. Wyss, M., & Kaddurah-Daouk, R. (2000). Creatine and creatinine metabolism. *Physiological Reviews, 80*(3), 1107–1213. https://doi.org/10.1152/physrev.2000.80.3.1107
6. Cunha, M. P., Martín-de-Saavedra, M. D., Romero, A., Egea, J., Ludka, F. K., Tasca, C. I., Farina, M., Rodrigues, A. L., & López, M. G. (2014). Both creatine and its product phosphocreatine reduce oxidative stress and afford neuroprotection in an in vitro Parkinson's model. *ASN Neuro, 6*(6), 1759091414554945. https://doi.org/10.1177/1759091414554945
7. Genius, J., Geiger, J., Bender, A., Möller, H. J., Klopstock, T., & Rujescu, D. (2012). Creatine protects against excitotoxicity in an in vitro model of neurodegeneration. *PLoS ONE, 7*(2), e30554. https://doi.org/10.1371/journal.pone.0030554
8. Benton, D., & Donohoe, R. (2011). The influence of creatine supplementation on the cognitive functioning of vegetarians and omnivores. *British Journal of Nutrition, 105*(7), 1100–1105. https://doi.org/10.1017/S0007114510004733
9. McMorris, T., Mielcarz, G., Harris, R. C., Swain, J. P., & Howard, A. (2007). Creatine supplementation and cognitive performance in elderly individuals. *Aging, Neuropsychology, and Cognition, 14*(5), 517–528. https://doi.org/10.1080/13825580600788100
10. Rawson, E. S., Lieberman, H. R., Walsh, T. M., Zuber, S. M., Harhart, J. M., & Matthews, T. C. (2008). Creatine supplementation does not improve cognitive function in young adults. *Physiology & Behavior, 95*(1–2), 130–134. https://doi.org/10.1016/j.physbeh.2008.05.009
11. Watanabe, A., Kato, N., & Kato, T. (2002). Effects of creatine on mental fatigue and cerebral hemoglobin oxygenation. *Neuroscience Research, 42*(4), 279–285. https://doi.org/10.1016/S0168-0102(02)00007-X
12. Turner, C. E., Byblow, W. D., & Gant, N. (2015). Creatine supplementation enhances corticomotor excitability and cognitive performance during oxygen deprivation. *Journal of Neuroscience, 35*(4), 1773–1780. https://doi.org/10.1523/JNEUROSCI.3113-14.2015
13. Greenamyre, J. T., & Hastings, T. G. (2004). Parkinson's—Divergent causes, convergent mechanisms. *Science, 304*(5674), 1120–1122. https://doi.org/10.1126/science.1098966
14. Writing Group for the NINDS Exploratory Trials in Parkinson Disease (NET-PD) Investigators. (2015). Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: A randomized clinical trial. *JAMA, 313*(6), 584–593. https://doi.org/10.1001/jama.2015.120
15. Shtilbans, A., Reintsch, W. E., Piscopo, V. E. C., Krahn, A. I., & Durcan, T. M. (2024). Combination of tauroursodeoxycholic acid, co-enzyme Q10 and creatine demonstrates additive neuroprotective effects in in vitro models of Parkinson's disease. *Frontiers in Neuroscience, 18,* 1492028. https://doi.org/10.3389/fnins.2024.1492028
16. Smith, A. N., Morris, J. K., Carbuhn, A. F., Herda, T. J., Keller, J. E., Sullivan, D. K., & Taylor, M. K. (2023). Creatine as a therapeutic target in Alzheimer's disease. *Current Developments in Nutrition, 7*(11), 102011. https://doi.org/10.1016/j.cdnut.2023.102011
17. Mao, X., Kelty, T. J., Kerr, N. R., Childs, T. E., Roberts, M. D., & Booth, F. W. (2021). Creatine supplementation upregulates mTORC1 signaling and markers of synaptic plasticity in the dentate gyrus while ameliorating LPS-induced cognitive impairment in female rats. *Nutrients, 13*(8), 2758. https://doi.org/10.3390/nu13082758
18. Snow, W. M., Cadonic, C., Cortes-Perez, C., Adlimoghaddam, A., Roy Chowdhury, S. K., Thomson, E., Anozie, A., Bernstein, M. J., Gough, K., Fernyhough, P., Suh, M., & Albensi, B. C. (2020). Sex-specific effects of chronic creatine supplementation on hippocampal-mediated spatial cognition in the 3xTg mouse model of Alzheimer's disease. *Nutrients, 12*(11), 3589. https://doi.org/10.3390/nu12113589

19. Taylor, M. K., Burns, J. M., Choi, I. Y., Herda, T. J., Lee, P., Smith, A. N., Sullivan, D. K., Swerdlow, R. H., & Wilkins, H. M. (2024). Protocol for a single-arm, pilot trial of creatine monohydrate supplementation in patients with Alzheimer's disease. *Pilot and Feasibility Studies, 10*(1), 42. https://doi.org/10.1186/s40814-024-01469-5
20. Ross, C. A., Aylward, E. H., Wild, E. J., Langbehn, D. R., Long, J. D., Warner, J. H., Scahill, R. I., Leavitt, B. R., Stout, J. C., Paulsen, J. S., Reilmann, R., Unschuld, P. G., Wexler, A., Margolis, R. L., & Tabrizi, S. J. (2014). Huntington disease: Natural history, biomarkers and prospects for therapeutics. *Nature Reviews Neurology, 10*(4), 204–216. https://doi.org/10.1038/nrneurol.2014.24
21. Andreassen, O. A., Dedeoglu, A., Ferrante, R. J., Jenkins, B. G., Ferrante, K. L., Thomas, M., Friedlich, A., Browne, S. E., Schilling, G., Borchelt, D. R., Hersch, S. M., Ross, C. A., & Beal, M. F. (2001). Creatine increases survival and delays motor symptoms in a transgenic animal model of Huntington's disease. *Neurobiology of Disease, 8*(3), 479–491. https://doi.org/10.1006/nbdi.2001.0406
22. Dedeoglu, A., Kubilus, J. K., Yang, L., Ferrante, K. L., Hersch, S. M., Beal, M. F., & Ferrante, R. J. (2003). Creatine therapy provides neuroprotection after onset of clinical symptoms in Huntington's disease transgenic mice. *Journal of Neurochemistry, 85*(6), 1359–1367. https://doi.org/10.1046/j.1471-4159.2003.01706.x
23. Hersch, S. M., Gevorkian, S., Marder, K., Moskowitz, C., Feigin, A., Cox, M., Como, P., Zimmerman, C., Lin, M., Zhang, L., Ulug, A. M., Beal, M. F., Matson, W., Bogdanov, M., Ebbel, E., Zaleta, A., Kaneko, Y., Jenkins, B., Hevelone, N., Zhang, H., Yu, H., Schoenfeld, D., Ferrante, R., & Rosas, H. D. (2006). Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. *Neurology, 66*(2), 250–252. https://doi.org/10.1212/01.wnl.0000194318.74946.b6
24. Hersch, S. M., Schifitto, G., Oakes, D., Bredlau, A. L., Meyers, C. M., Nahin, R., Rosas, H. D., & Huntington Study Group CREST-E Investigators and Coordinators. (2017). The CREST-E study of creatine for Huntington disease: A randomized controlled trial. *Neurology, 89*(6), 594–601. https://doi.org/10.1212/WNL.0000000000004209
25. Hardiman, O., Al-Chalabi, A., Chio, A., Corr, E. M., Logroscino, G., Robberecht, W., Shaw, P. J., Simmons, Z., & van den Berg, L. H. (2017). Amyotrophic lateral sclerosis. *Nature Reviews Disease Primers, 3,* 17071. https://doi.org/10.1038/nrdp.2017.71
26. Goodall, E. F., & Morrison, K. E. (2006). Amyotrophic lateral sclerosis (motor neuron disease): Proposed mechanisms and pathways to treatment. *Expert Reviews in Molecular Medicine, 8*(11), 1–22. https://doi.org/10.1017/S1462399406010854
27. Klivenyi, P., Ferrante, R. J., Matthews, R. T., Bogdanov, M. B., Klein, A. M., Andreassen, O. A., Mueller, G., Wermer, M., Kaddurah-Daouk, R., & Beal, M. F. (1999). Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. *Nature Medicine, 5*(3), 347–350. https://doi.org/10.1038/6568
28. Shefner, J. M., Cudkowicz, M. E., Schoenfeld, D., Conrad, T., Taft, J., Chilton, M., Urbinelli, L., Qureshi, M., Zhang, H., Pestronk, A., Caress, J., Donofrio, P., Sorenson, E., Bradley, W., Lomen-Hoerth, C., Pioro, E., Rezania, K., Ross, M., Pascuzzi, R., Heiman-Patterson, T., Tandan, R., Mitsumoto, H., Rothstein, J., Smith-Palmer, T., MacDonald, D., & Burke, D.; NEALS Consortium. (2004). A clinical trial of creatine in ALS. *Neurology, 63*(9), 1656–1661. https://doi.org/10.1212/01.wnl.0000142992.81995.f0
29. Pastula, D. M., Moore, D. H., & Bedlack, R. S. (2012). Creatine for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database of Systematic Reviews, 2012*(12), CD005225. https://doi.org/10.1002/14651858.CD005225.pub3
30. Lépine, J. P., & Briley, M. (2011). The increasing burden of depression. *Neuropsychiatric Disease and Treatment, 7*(Suppl 1), 3–7. https://doi.org/10.2147/NDT.S19617
31. Ahn, N. R., Leem, Y. H., Kato, M., & Chang, H. K. (2016). Effects of creatine monohydrate supplementation and exercise on depression-like behaviors and raphe 5-HT neurons in mice. *Journal of Exercise Nutrition and Biochemistry, 20*(3), 24–31. https://doi.org/10.20463/jenb.2016.09.20.3.4
32. Cunha, M. P., Pazini, F. L., Rosa, J. M., Ramos-Hryb, A. B., Oliveira, Á., Kaster, M. P., & Rodrigues, A. L. (2015). Creatine, similarly to ketamine, affords antidepressant-like effects in the tail suspension test via adenosine A_1 and A_2A receptor activation. *Purinergic Signalling, 11*(2), 215–227. https://doi.org/10.1007/s11302-015-9446-7
33. Kanekar, S., Ettaro, R., Hoffman, M. D., Ombach, H. J., Brown, J., Lynch, C., Sheth, C. S., & Renshaw, P. F. (2021). Sex-based impact of creatine supplementation on depressive symptoms, brain serotonin and SSRI efficacy in an animal model of treatment-resistant depression. *International Journal of Molecular Sciences, 22*(15), 8195. https://doi.org/10.3390/ijms22158195
34. Leem, Y. H., Kato, M., & Chang, H. (2018). Regular exercise and creatine supplementation prevent chronic mild stress-induced decrease in hippocampal neurogenesis via Wnt/GSK3β/β-catenin pathway. *Journal of Exercise Nutrition and Biochemistry, 22*(2), 1–6. https://doi.org/10.20463/jenb.2018.0009
35. Kim, S., Hong, K. B., Kim, S., Suh, H. J., & Jo, K. (2020). Creatine and taurine mixtures alleviate depressive-like behaviour in *Drosophila melanogaster* and mice via regulating Akt and ERK/BDNF pathways. *Scientific Reports, 10*(1), 11370. https://doi.org/10.1038/s41598-020-68424-1

36. Kondo, D. G., Forrest, L. N., Shi, X., Sung, Y. H., Hellem, T. L., Huber, R. S., & Renshaw, P. F. (2016). Creatine target engagement with brain bioenergetics: A dose-ranging phosphorus-31 magnetic resonance spectroscopy study of adolescent females with SSRI-resistant depression. *Amino Acids, 48*(8), 1941–1954. https://doi.org/10.1007/s00726-016-2194-3
37. 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, 125*(2), 247–257. https://doi.org/10.1007/s00702-017-1817-5
38. Kious, B. M., Sabic, H., Sung, Y. H., Kondo, D. G., & Renshaw, P. (2017). An open-label pilot study of combined augmentation with creatine monohydrate and 5-hydroxytryptophan for selective serotonin reuptake inhibitor- or serotonin-norepinephrine reuptake inhibitor-resistant depression in adult women. *Journal of Clinical Psychopharmacology, 37*(5), 578–583. https://doi.org/10.1097/JCP.0000000000000754
39. Chen, Y., Cao, X., Zang, W., Tan, S., Ou, C. Q., Shen, X., Gao, T., & Zhao, L. (2019). Intravenous administration of adenosine triphosphate and phosphocreatine combined with fluoxetine in major depressive disorder: Protocol for a randomized, double-blind, placebo-controlled pilot study. *Trials, 20*(1), 34. https://doi.org/10.1186/s13063-018-3115-4
40. Tran, K. H., Luki, J., Hanstock, S., Hanstock, C. C., Seres, P., Aitchison, K., & Le Melledo, J. M. (2023). Decreased GABA+ ratios referenced to creatine and phosphocreatine in the left dorsolateral prefrontal cortex of females of reproductive age with major depression. *Journal of Psychiatry & Neuroscience, 48*(4), E285–E294. https://doi.org/10.1503/jpn.230016
41. Henigsberg, N., Šarac, H., Radoš, M., Radoš, M., Ozretić, D., Foro, T., Erdeljić Turk, V., Hrabač, P., Bajs Janović, M., Rak, B., & Kalember, P. (2017). Lower choline-containing metabolites/creatine (Cr) rise and failure to sustain NAA/Cr levels in the dorsolateral prefrontal cortex are associated with depressive episode recurrence under maintenance therapy: A proton magnetic resonance spectroscopy retrospective cohort study. *Frontiers in Psychiatry, 8,* 277. https://doi.org/10.3389/fpsyt.2017.00277
42. Forbes, S. C., Cordingley, D. M., Cornish, S. M., Gualano, B., Roschel, H., Ostojic, S. M., Rawson, E. S., Roy, B. D., Prokopidis, K., Giannos, P., & Candow, D. G. (2022). Effects of creatine supplementation on brain function and health. *Nutrients, 14*(5), 921. https://doi.org/10.3390/nu14050921
43. Vagnozzi, R., Signoretti, S., Floris, R., Marziali, S., Manara, M., Amorini, A. M., Belli, A., Di Pietro, V., D'Urso, S., Pastore, F. S., Lazzarino, G., & Tavazzi, B. (2013). Decrease in N-acetylaspartate following concussion may be coupled to decrease in creatine. *Journal of Head Trauma Rehabilitation, 28*(4), 284–292. https://doi.org/10.1097/HTR.0b013e3182795045
44. Signoretti, S., Di Pietro, V., Vagnozzi, R., Lazzarino, G., Amorini, A. M., Belli, A., D'Urso, S., & Tavazzi, B. (2010). Transient alterations of creatine, creatine phosphate, N-acetylaspartate and high-energy phosphates after mild traumatic brain injury in the rat. *Molecular and Cellular Biochemistry, 333*(1–2), 269–277. https://doi.org/10.1007/s11010-009-0228-9
45. Sullivan, P. G., Geiger, J. D., Mattson, M. P., & Scheff, S. W. (2000). Dietary supplement creatine protects against traumatic brain injury. *Annals of Neurology, 48*(5), 723–729. https://doi.org/10.1002/ana.410480515
46. Ainsley Dean, P. J., Arikan, G., Opitz, B., & Sterr, A. (2017). Potential for use of creatine supplementation following mild traumatic brain injury. *Concussion, 2*(2), CNC34. https://doi.org/10.2217/cnc-2016-0016
47. Sakellaris, G., Kotsiou, M., Tamiolaki, M., Kalostos, G., Tsapaki, E., Spanaki, M., Spilioti, M., Charissis, G., & Evangeliou, A. (2006). Prevention of complications related to traumatic brain injury in children and adolescents with creatine administration: An open label randomized pilot study. *Journal of Trauma, 61*(2), 322–329. https://doi.org/10.1097/01.ta.0000230269.46108.d5
48. Sakellaris, G., Nasis, G., Kotsiou, M., Tamiolaki, M., Charissis, G., & Evangeliou, A. (2008). Prevention of traumatic headache, dizziness and fatigue with creatine administration: A pilot study. *Acta Paediatrica, 97*(1), 31–34. https://doi.org/10.1111/j.1651-2227.2007.00529.x
49. Sakellaris, G., Partalis, N., Nasis, G., Kotsiou, M., Tamiolaki, M., Bouloukaki, E., & Evangeliou, A. (2012). Outcome of traumatic dysarthria and lingual problems of understanding with creatine administration: An open label randomized pilot study. *Journal of Trauma & Treatment, 1,* 120. https://doi.org/10.4172/2167-1222.1000120
50. Gerbatin, R. R., Silva, L. F. A., Hoffmann, M. S., Della-Pace, I. D., do Nascimento, P. S., Kegler, A., de Zorzi, V. N., Cunha, J. M., Botelho, P., Neto, J. B. T., Furian, A. F., Oliveira, M. S., Fighera, M. R., & Royes, L. F. F. (2019). Delayed creatine supplementation counteracts reduction of GABAergic function and protects against seizure susceptibility after traumatic brain injury in rats. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 92,* 328–338. https://doi.org/10.1016/j.pnpbp.2019.02.004
51. Saraiva, A. L., Ferreira, A. P., Silva, L. F., Hoffmann, M. S., Dutra, F. D., Furian, A. F., Oliveira, M. S., Fighera, M. R., & Royes, L. F. (2012). Creatine reduces oxidative stress markers but does not protect against seizure susceptibility after severe traumatic brain injury. *Brain Research Bulletin, 87*(2–3), 180–186. https://doi.org/10.1016/j.brainresbull.2011.10.010