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Molecular mechanisms underlying the effects of regular exercise on substance use disorder-associated cognitive impairment and dementia risk: A narrative review

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ABSTRACT

Dementia is one of the most widespread neurodegenerative conditions worldwide and is accompanied by cell death in the central nervous system (CNS). Risk factors include age, genetics, CNS trauma, cardiovascular disease, environmental factors, and stressors. Stress, especially oxidative stress, disrupts mitochondrial respiration, causing mitochondrial damage in neurodegenerative illnesses like dementia. The role of oxidative stress in dementia progression has been studied recently. As a progressive disorder, addiction may be a stressor that induces oxidative stress. The psychological and psychophysiological effects of addiction can exacerbate oxidative stress, neuronal death, and dementia progression. Identifying an effective alternative therapy to prevent oxidative stress-induced dementia development could be advantageous. Exercise reverses dementia progression by lowering oxidative stress-related neuropathological alterations in addiction. Regular exercise can help overcome addiction's cognitive effects in a complementary, affordable, and accessible way.

This review will discuss dementia progression and oxidative stress-induced dysfunction. We will also examine addiction as an oxidative stressor in this neurodegenerative illness. To this end, we searched PubMed and Google Scholar for articles published between 2015 and 2025 using the keywords dementia, cognitive impairment, exercise, physical activity, addiction, METH, and oxidative stress. Finally, the last part of the review provides information to improve the current understanding of the role of regular exercise in the progression of substance use disorder-associated cognitive impairment and dementia risk.

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Introduction

Dementia

Dementia, the most prevalent form of neurodegenerative disease, is the most common form of degenerative neurological condition and is primarily experienced by older individuals. Dementia is rapidly becoming one of the pressing health concerns of the 21st century. A mental decline that interferes with daily life is referred to as dementia. It is a group of symptoms that affect cognitive function rather than a single disease. Symptoms include changes in mood and behavior, memory loss, and communication problems. Several disorders can bring on dementia, and the underlying reason affects how severe and how quickly it progresses (1). Several types of dementia have been identified, each with distinct pathogenesis, presentation, and trajectory. The following is a list of the different types of dementia: degenerative dementias, vascular dementia (VaD), and mixed dementia (2). The three groups of degenerative dementias include features associated with the cortical, subcortical, and both regions. Dementia symptoms progress at different rates across cognitive, behavioral, and functional domains, depending on the individual (3). This diversity makes it hard to create a universal staging tool. In general, dementia is classified into mild, moderate, and severe stages to reflect symptom severity (4). Depending on the cause and stage, dementia symptoms may include: Memory loss, particularly recent events and discussions; language and communication issues, including trouble finding the proper words or understanding others; reasoning and judgment issues, including decision-making and problem-solving; depression, anxiety, agitation, and personality changes; disinterest in past hobbies; losing your way in familiar locations; not recognizing familiar people or objects; motor coordination issues, insomnia, and daytime drowsiness (5).

The most prevalent type of dementia is Alzheimer's disease (AD) (6). AD leads to a decline in cognitive abilities,

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such as memory impairment, which ultimately culminates in mortality (7). The hallmarks of this disease are extracellular accumulation of amyloid beta (Aβ) peptides (Aβ plaques) in senile plaques (SP) and intracellular deposition of hyperphosphorylated tau protein in neurofibrillary tangles (NFT) in the hippocampus and neocortex. Both of these aberrant proteins are found in the areas of the brain that are affected by AD (8). Cerebral cortex anomalies, such as afferent or efferent impairments or a lack of neuromodulators, are associated with the subcortical type of dementia. Memory loss, sluggish thought, emotional alternation, personality changes, and an inability to comprehend information are all symptoms of this type of dementia (9). For instance, the loss of nerve cells in the substantia nigra is the main cause of Parkinson's disease (PD). As a result, dopamine (DA), the main neuromodulator, is significantly diminished because dopaminergic neurons in this area die. DA coordinates movement and motor control. Memory, attention, and visual perception impairments are common among the clinical signs of PD and get worse as the condition progresses. In addition, dementia with Lewy bodies (LB), thought to be the second most frequent type of dementia, is defined pathophysiologically by LB accumulation in the amygdala and other brain regions (10). In the clinical setting, people with PD often show memory abnormalities, as well as earlier and more significant visuospatial impairments, visual hallucinations, sensitivity to neuroleptics, and ultimately Parkinsonian movement symptoms (10). On the other hand, VaD is a condition associated with cognitive abnormalities including speech impairment, seizures, lesions in the white matter, aberrant gait patterns, incontinence, and Parkinsonism. VaD develops as a result of multiple cortical infarcts, subcortical cerebrovascular alterations, or a single vascular event, such as a stroke. The three main risk factors for VaD are generally regarded as atherosclerotic disorders, microbleeds, and strokes (11).

Taken together, due to the high rate of dementia incidence worldwide and its burden on societies, it is important to understand the exact mechanism of dementia pathology to develop an alternative therapeutic strategy to overcome the destructive nature of this disorder spectrum.

Oxidative stress role in pathogenesis of dementia

Based on our knowledge, dementia is a multifactorial disorder spectrum, and its exact pathophysiology is unknown. Various endogenous or exogenous factors such as age, genetic state, central nervous system (CNS) injuries, cardiovascular disorders, lifestyle, elevated inflammation, and disrupted mitochondrial function accompanied by overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress, are the most important risk factors involved (12). There is growing evidence indicating that the latter, oxidative stress, has a conspicuous role in the pathogenesis of dementia and other neurodegenerative disorders, including PD, AD, and stroke (13).

The nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) enzymes transfer electrons across the plasma membrane to molecular oxygen. This electron transfer, in turn, produces superoxide anion and, eventually, ROS. There are several types of ROS, including hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH) (14). Although ROS are produced at low levels under normal physiological conditions, their accumulation may cause oxidative stress and, under severe conditions, neural dysfunction or even cell death. Physiological concentrations of ROS/RNS produced by normal cellular metabolism are essential for regular cell functions, including cell signaling (15). There is a balance between ROS production and destruction. A network of anti-oxidant defense systems within cells seems to minimize ROS generation and the likelihood of oxidative damage. It is fascinating to consider how the body regulates itself to maintain this delicate oxidation-anti-oxidant balance. Anti-oxidants function in a coordinated manner to protect against oxidative stress when a balanced anti-oxidant system is present (16). This defense mechanism involves several CNS cells, including neurons, astrocytes, pericytes, microglia, and endothelial cells, that help maintain physiological ROS levels (17). Indeed, oxidative stress results from a loss of balance in ROS/nitric oxide synthase (NOS) levels under physiological conditions (15). Several anti-oxidant strategies can protect against ROS-induced toxicity. For instance, certain agents, such as catalase (CAT), can convert ROS into less active molecules, preventing their transformation into more harmful forms (18)alcohol, marijuana, opioids, cocaine., etc,. Anti-oxidant enzymes such as superoxide dismutase, CAT, and glutathione peroxidase (GPx) convert ROS into less active molecules. These mechanisms can inhibit transcription factors, protect against oxidative stress, regulate cell death, and reduce protein oxidation (19).

Several cellular compartments, such as peroxisomes, contribute to ROS generation, although ROS production mainly occurs in mitochondria (20). Hence, mitochondria have a key role in oxidative stress-induced neuronal damage. From a biochemical perspective, ROS can be considered byproducts of mitochondrial adenosine triphosphate (ATP) production. This process, which is accompanied by oxidative phosphorylation, produces OH. According to the literature, OH is the most destructive oxidant (20). Accumulation of ROS in the cell damages both mitochondrial and nuclear deoxyribonucleic acid (DNA), proteins, and even lipids. Among these molecules, proteins seem most susceptible to ROS action, leading to their degradation (21). On the other hand, ROS can activate several transcription factors, such as tumor suppressor 53 (p53), nuclear factor kappa B (NF-κB), and hypoxia-inducible factor 1-alpha (HIF-1α), and therefore induce apoptosis, stress resistance, or senescence (22). ROS destructive effects are not limited to proteins. ROS-induced lipid peroxidation disrupts the neuronal lipid bilayer (23). ROS-induced DNA alterations also include nitrogenous base damage, DNA strand breaks, and various mutations (21). In addition, oxidative stress can impair metabolism and Ca^{2+} homeostasis, as well as transcription and translation (24). There are several studies indicating that mitochondrial damage, neural death, and subsequently oxidative stress are involved in several types of dementia (25). On the other hand, endothelial cells and pericytes, which form the blood-brain barrier (BBB), limit the entry of neurotoxic proteins derived from plasma, metals, pathogens, erythrocytes, and leucocytes into the brain. Oxidative stress can increase BBB permeability, allowing neurotoxic blood-derived factors to enter the brain and contribute to synaptic and neuronal injury (26). Preclinical studies show that BBB leakage leads to neurotoxin accumulation in the brain. Fibrin, thrombin, hemoglobin, iron-containing

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hemosiderin, free iron, and/or plasmin are some examples. These toxins induce neurotoxicity and subsequently progressive neurodegeneration via oxidative stress (27).

In addition, neural loss and demyelination have been shown following CNS exposure to oxidative stress and inflammation (28). This condition results in peroxynitrite production and consequently leads to severe neural damage and several types of dementia. In PD dementia, ROS-induced dopaminergic neurodegeneration is mediated by matrix metalloproteinase-3 (MMP3) (29). For example, increased 8-hydroxy-2′-deoxyguanosine (8OHdG) levels following DNA oxidation or increased 3-nitrotyrosine (3-NT) levels following protein oxidation have been shown in AD patients. These alterations may precede Aβ plaque formation (28). In addition, identifying specific targets of protein oxidation, such as peptidyl prolyl cis-trans isomerase (PPI), emphasizes the role of protein oxidation in the hippocampus of AD patients (29). In addition, increased levels of malondialdehyde (MDA), a marker for lipid peroxidation, along with decreased levels of glutathione (GSH) and glutathione reductase (GR), have been observed in AD patients (30). Moreover, Aβ deposition up-regulates the receptor for advanced glycation end products (RAGE) (31). On the other hand, RAGE up-regulation activates NADPH oxidases, ultimately leading to excessive ROS generation and, consequently, ROS-induced neural damage in AD patients (30). Besides, increased levels of ROS and RNS have been shown in dementia; oxidative stress-induced damage leads to cognitive dysfunction (32). Indeed, inhibiting oxidative stress may reverse cognitive dysfunction. However, clinical trials using vitamin E or other anti-oxidants have not shown promising results (29). Taken together, this growing evidence suggests that oxidative stress may have a critical role in the etiopathogenesis of dementia and other neurodegenerative disorders. Given the relative failure of current treatments, other therapies such as regular exercise, due to its anti-oxidant effects, may be a potential alternative for combination therapy.

Addiction as an oxidative stress driver

Drug abuse can be defined as the repeated use of drugs despite their negative effects (33). Addiction is at the top of the social harms in the world. Generally, more than 230 million people worldwide are suffering from substance abuse, with a mortality rate of nearly two hundred thousand annually. According to the reports of the United Nations Office on Drugs and Crime (UNODC), only one in every eight addicted individuals receives treatment for substance use disorder (SUD) (34).

DA signaling in the reward pathway (i.e., nucleus accumbens (NAc), ventral tegmental area (VTA), prefrontal cortex (PFC) is thought to be a primary mechanism that motivates drug use during early "non-addicted" stages, in which drug exposure is initiated. Furthermore, the basal ganglia (BG) are involved in addiction and responsible for the formation of habitual substance taking. Additionally, the extended amygdala, which is affected by stress and generally associated with substance withdrawal, as well as the PFC, responsible for executive functions, including the control of substance intake, contribute to the progression of addiction (35).

Addiction can be described with three stages: 1. Binge/intoxication; the individual consumes an intoxicating substance and experiences its rewarding effects. 2. Withdrawal/negative affect; the individual experiences a negative emotional state in the absence of the substance. 3. Preoccupation/anticipation; the individual relapses after a period of abstinence. It is well known that long-term use of drugs like morphine, alcohol, and methadone increases the risk of cognitive impairment and dementia (36).

As mentioned earlier, there are several mechanisms implicated in dementia progression, but addiction-induced oxidative stress is a significant factor affecting cognitive impairments and later aging and dementia. Some studies show that drug abuse-induced oxidative stress leads to cognitive impairment and subsequently symptoms of dementia. Many studies have demonstrated that alcohol, morphine, heroin, amphetamine (AMPH), cocaine, and marijuana exposure significantly increase the levels of oxidants, such as ROS and lipoperoxides, along with a decrease in the levels of anti-oxidants (37). For example, AMPH may alter those neurosubstrates linked with the underlying mechanism of dementia through its central effects. These neurosubstrates include the Aβ cascade, tau protein, oxidative stress, and brain inflammation, all of which are time-consuming processes (38). AMPH activates microglia, which may be linked to chronic inflammation, and chronic inflammation may play a role in the pathophysiology of AD and VaD (38). Although oxidative imbalance has been linked to cognitive impairment in methamphetamine (METH)-dependent persons, the evidence currently available does not prove that oxidative stress is the direct cause of dementia (39).

Alcohol consumption, for instance, causes brain damage and progression of alcohol-related dementia (ARD) through the generation of acetaldehyde metabolites (38). Alcohol consumption may also increase dementia risk through induction of neuronal toxicity, thiamine deficiency, and dysfunction of the liver and immune system (40). Alcohol-induced ROS production and inflammatory response cause neuronal loss, particularly in the limbic system (38). Principally, endogenous anti-oxidants such as GSH clear ROS products, although acute and chronic alcohol consumption reduces brain GSH levels. Eventually, chronic ROS production in the brain causes neuronal dysfunction and death, which later leads to neurodegenerative conditions such as dementia (41). On the other hand, METH, another abused substance, causes neurotoxic effects by altering the neurotransmitter systems (42). ROS production and oxidative stress may play a role in METH-induced neurotoxicity. METH abuse leads to an imbalance in ROS production and anti-oxidant function (41). In addition, it has been revealed that cocaine or METH abusers showed a reduced anti-oxidative response compared to the control subjects. Moreover, permanent reduction in global and regional cerebral blood flow and METH-related cerebrovascular dysfunction have occurred even after two years of METH abstinence. On the other hand, psychostimulants and tobacco have extreme pro-oxidant effects and remarkably activate endothelial oxidative stress responses. Hence, both of them impair the structure and function of the BBB in the dense microcapillary network of the brain (43). In addition, one study indicates that treating the human neuroblastoma cell line SH-SY5Y with morphine leads to ROS and RNS production, along with a time- and concentration-dependent decrease in μ-opioid receptor (MOR) messenger ribonucleic acid (mRNA) levels (41). Additionally, oxidative stress levels were increased in the

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hippocampus and prefrontal cortex of morphine-dependent rats (37). In this manner, chronic use of marijuana increases the risk of dementia, in which the duration of marijuana abuse is correlated with the severity of learning and memory impairments (44).

In general, substance abuse is related to a decrease in brain volume in cortical regions and, consequently, cognitive dysfunction (35). In this regard, Numerous genes whose mutations or polymorphisms increase the risk of PD are linked to mitochondrial function, providing substantial evidence that mitochondrial dysfunction contributes to Parkinson's-induced dementia (40). METH exposure may contribute to cognitive and dementia-related pathology by disrupting mitochondrial function and increasing oxidative stress (45).

Taken together, increased ROS production following drug abuse plays a key role in the neuropathology of dementia and other neurodegenerative disorders. There is growing evidence that hippocampal dysfunction and altered neurotransmitter signaling are closely associated with addiction-related cognitive impairments. According to research by Jafari-Sabet *et al*., dorsal hippocampal gamma-aminobutyric acid (GABA) and N-methyl-D-aspartate (NMDA) receptor signaling, as well as nitric oxide pathways, are involved in memory processes associated with ethanol and tramadol (46). The scientific plausibility of cognitive impairment linked to substance use is further supported by recent research that has emphasized the involvement of drug-induced neurotoxicity and neuroprotection (47). In chronic drug abuse, the anti-oxidant system of the brain is down-regulated, and the physiological balance is disrupted; hence, several types of neuropathologies, including dementia, will progress (48). It seems that any complementary therapy which could attenuate the levels of addiction-induced oxidative stress may play a critical role in dementia prevention or amelioration of the symptoms.

Regular exercise as potential treatment for substance use disorder-associated cognitive impairment and dementia risk by reducing oxidative stress

According to extensive clinical trials, exercise is a cost-effective strategy that can greatly reduce the burden of numerous diseases, including but not limited to cardiovascular diseases, cancers, diabetes, sarcopenia, and neuropsychiatric disorders (49). Long-term research has been done on the benefits of physical activity on brain functions as a non-drug strategy for preserving brain health, treating neurodegenerative disorders, and enhancing cognitive functions such as spatial learning and memory, anxiety, depressive-like behavior, etc. (50). It is complicated to find an alternative therapeutic approach for substance addiction treatment, as the disease's underlying neurobiology changes over time during its progression; hence, it is imperative to develop new and more efficient treatments (51). Physical activity might influence oxidative and neurobiological mechanisms linked to substance use disorders; yet, its therapeutic outcomes are probably contingent upon the intensity of exercise, individual patient traits, and the treatment environment. In the subsequent segment of this essay, we will concentrate on the impact of exercise as an adjunctive strategy for mitigating cognitive impairments in individuals with addiction.

Physical activity, and specifically exercise, can play a role as a complementary method in improving cognitive side effects caused by addiction. There has been some evidence that exercise could be used either as a standalone intervention or combined with other therapeutic approaches to treat addiction-induced alterations. Exercise appears to address the systems involved in the addiction process at both early and late stages, in addition to other health benefits (e.g., preventing obesity and secondary diseases such as diabetes) (52).

In recent years, the body of information on exercise and oxidative stress has expanded tremendously. It has now been shown that contractile, inactive skeletal muscles generate ROS and NOS (53). Researchers have discussed the harmful effects of ROS; nevertheless, adequate levels of active oxidative chemicals are also required. As mentioned earlier, although appropriate oxidant concentrations regulate many cellular communication pathways and gene expression, including transcription, mRNA stability, epigenetic regulation, and signal transmission, excessive exercise damages contracting muscle cells through oxidative processes (52). Furthermore, exercise influences the production of a wide variety of products associated with genes that regulate oxidative processes. These adaptations may support cellular maintenance and recovery during repeated exercise exposure (54). Enzymatic and nonenzymatic anti-oxidants in muscle fibers work together to eliminate ROS. These anti-oxidants are compartmentalized within various organelles and the fiber's cytoplasm. In addition, both enzymatic and nonenzymatic anti-oxidants exist in the vascular system and the extracellular region. These anti-oxidants protect muscle fibers from oxidative stress during times of high oxidant levels (18).

There are various intracellular mechanisms responsible for the positive effects of exercise on brain function, including the repair of neuronal damage caused by substance abuse-induced oxidative stress (55). Preclinical research suggests that regular exercise may improve anti-oxidant defenses and mitochondrial biogenesis, with possible benefits for brain function and specific cognitive outcomes (56). It also up-regulates the activity of proteasome complexes and targets of rapamycin (mTOR) in the brain (57). Several studies show that neurons have high levels of polyunsaturated fatty acids, high metabolic rates, and high oxygen consumption; however, they have low anti-oxidant capacity. As a result, neurons are susceptible to oxidative damage. Activating the nuclear factor erythroid 2–related factor 2/anti-oxidant response element (Nrf2/ARE) pathway is required to trigger anti-oxidant defense after oxidative damage. The adaptive anti-oxidant effects of exercise involve Nrf2 activation as a critical phase (58). Exercise-related activation of the Nrf2/ARE pathway may contribute to adaptive anti-oxidant responses, although the magnitude of this effect may vary according to exercise dose and clinical status. Moderate exercise can exert systemic anti-oxidant effects by activating Nrf2, a process that can occur in several tissues. Nrf2 activation is not limited to skeletal and/or cardiac muscle; it can also occur in the brain, liver, and kidneys (59). The proposed mechanisms underlying oxidative stress-induced neurobiological dysfunction in substance use disorders and the potential protective effects of regular exercise are summarized in Figure 1.

In a research study, Zhang *et al*. investigated the effects of aerobic activity on cognitive disorders and oxidative stress in people addicted to METH. They discovered that METH

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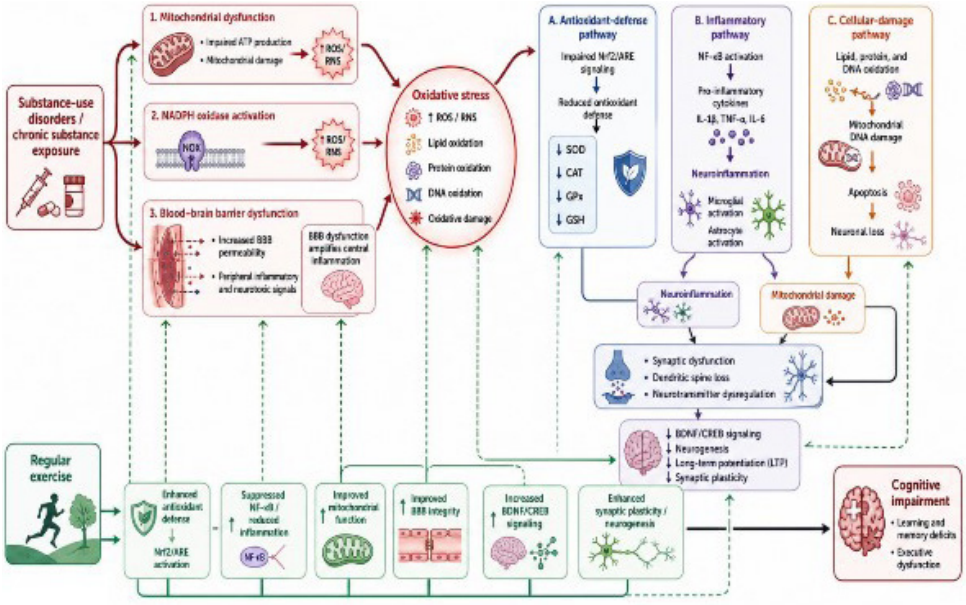


Figure 1. Mechanism relating neurobiological dysfunction to substance-use disorders and the possible therapeutic benefit of regular exercise
A multi-level pathogenic cascade centered on oxidative stress is initiated by prolonged drug exposure. Substance abuse disrupts the blood–brain barrier, overactivates nicotinamide adenine dinucleotide phosphate oxidase, and impairs upstream mitochondrial function, all of which contribute to an imbalance in reactive oxygen species/reactive nitrogen species production. This central hub of oxidative stress triggers a tripartite downstream response: (1) impairment of the nuclear factor erythroid 2/ antioxidant response element antioxidant defense system; (2) activation of the nuclear factor kappa B -mediated inflammatory pathway resulting in neuroinflammation and glial activation; and (3) severe cellular damage via macromolecular oxidation (lipid, protein, and DNA). These convergent processes lead to synaptic dysfunction, neuronal death, and defective neuroplasticity, typified by decreased brain-derived neurotrophic factor/cAMP response element-binding protein signaling and long-term potentiation deficits. Frequent exercise is a powerful modulator that may counteract these mechanisms by protecting neurotrophic signaling pathways, reducing neuroinflammation, and increasing antioxidant capacity.

-dependent patients have verbal learning and memory deficits as well as high oxidative stress levels in their blood. The researchers also showed that aerobic exercise improves processing speed and reduces the lipid peroxidation biomarker MDA in METH addicts (39). In fact, METH is capable of causing chronic deficiencies in the dopaminergic and serotoninergic systems. This is primarily because accumulated DA is prone to autoxidation and generates DA-quinones, both of which can damage and inhibit macromolecular function (60). Accordingly, exercise-related mitochondrial adaptations may help support cellular energy metabolism and neuronal resilience. In the cited METH -related evidence, exercise was associated with lower protein carbonyl levels and improved CAT-related antioxidant function (59). Exercise, on the other hand, limited ROS production, thereby decreasing protein carbonyl (PC) damage. This was found not only in the Na^+K^+-ATPase and CAT, but also in the hippocampus, where their functions were restored. In light of these findings, Na+K+-ATPase plays a crucial role in cellular function, specifically in regulating ion exchange between cells and the intercellular space (61).

The effects of exercise on DA uptake are modulatory, particularly when oxidative processes have damaged the dopamine transporter as a result of an excess of striatal dopaminergic activity (62). ROS production and oxidative status are naturally boosted by aerobic cellular metabolism and, as a result, play a significant role in regulating signal transduction pathways and gene expression (63). However, when a factor such as AMPH increases ROS production, excess ROS may damage macromolecules such as proteins, membrane lipids, and DNA, ultimately leading to neuronal death in the brain (64). Exercise's ability to maintain physiological oxidative status in the hippocampus further supports its modulatory role in brain regions particularly vulnerable to AMPH damage. In this view, engaging in regular physical exercise can be helpful as an adjuvant therapy to prevent relapses of psychostimulant drug use, hence decreasing the detrimental effects of addiction (65).

In addition, physical activity may affect brain plasticity through mechanisms that are concentrated on the modification of chromatin in regions that have been linked to addictive drug behavior (66). Exercise can help prevent glutamate receptor overstimulation that can occur after long-term medication use. Forced and voluntary running lowers glutamate levels in the striatum and hippocampus of normal animals (67). Additionally, data showing that forced treadmill running increases striatal metabotropic glutamate receptor 2/3 (mGluR2/3) expression, which dampens glutamatergic transmission, provide evidence that exercise induces plastic alterations in glutamate receptors (68). This effect can be blocked by concurrent activation of glutamate NMDA and dopamine D1 receptors, which raises the possibility that the effects of exercise on excessive drug self-administration and the development of addiction may require modulation of both dopaminergic and glutamatergic signaling. Forced running also increases striatal Fos expression, which is a marker of functional activity (69). There is a drop in dopaminergic activity throughout the reward pathway during the early withdrawal period, and this decrease in activity has been associated with withdrawal symptoms such as anhedonia, negative affect, and desire (70). Regular exercise has the potential to correct hypofunctioning in the mesolimbic system, which develops in the early stages of drug withdrawal after prolonged drug exposure. Recent research lends further credence to this concept by demonstrating that engaging in voluntary wheel running reduces the amount of damage caused by METH to DA and serotonin terminals in the striatum (71).

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Exercising has also been demonstrated to promote gliogenesis in the PFC, which may help counteract the deficiencies in executive function that are associated with an increased risk of relapsing from METH and other narcotics (72). Additionally, persistent inflammation, which obesity and possibly SUDs can trigger, may disrupt insulin-like growth factor 1 (IGF-1) and brain-derived neurotrophic factor (BDNF) signaling, resulting in neurotrophin resistance through increased pro-inflammatory cytokines like interleukin-1 beta (IL-1β) (65).

Additionally, assisted or forced exercise may increase BDNF levels, possibly driven by increased DA in the dorsal striatum (67). A study by Choi *et al.* on VaD showed that four weeks of forced treadmill activity after chronic cerebral hypoperfusion (CCH) increased cognitive function and hippocampal neurogenesis through a mechanism involving BDNF and phosphorylated cAMP response element-binding protein (pCREB). In AD, VaD, and post-stroke hypoperfusion, CCH is significantly associated with the severity of memory impairment and the loss in cerebral blood flow. In the two-vessel occlusion (2VO) animal model, it has been shown that CCH causes memory impairment through increasing oxidative stress in the hippocampus, hippocampal neurodegeneration, neuroinflammation, and reduced cerebral blood flow (29). Exercise can improve long-term potentiation (LTP) damage by raising the slope of field excitatory postsynaptic potential (fEPSP), as indicated by the findings of four studies that were incorporated into the analysis (73). Exercise has been linked to increased calcium/calmodulin-dependent protein kinase IV (CaMKIV) availability, which in turn promotes CREB phosphorylation and CREB-mediated transcription. These findings come from Western blotting and *in vivo* electrophysiology (67).

Regular exercise stimulates the same reward pathways as illegal narcotics do by increasing DA release and DA receptor activation (74). In addition, physical activity may influence brain plasticity via mechanisms involved in the remodeling of chromatin in brain regions which are associated with addiction (75). Despite these encouraging findings, some workouts may be inefficient or contribute to unfavorable outcomes. One study found that aerobic activity may increase oxidative stress (76). Further research has shown that acute aerobic exercise raises oxidative stress and lowers anti-oxidant levels (77). In this regard, studies report that anaerobic exercise increases oxidative stress and either decreases or increases anti-oxidant levels. Additionally, full-body resistance training increased oxidative damage. In one study, high-load resistance exercise increased blood MDA, whereas exercise effects varied by exercise type, intensity, duration, and training status (78). Although the previous study found that resistance training did not reduce oxidative stress, different combinations of resistance exercise did reduce oxidative stress-related damage, possibly because of specific oxidative damage markers and the individual's training status. Aerobic exercise, rather than resistance training, is more effective at reducing the negative effects of oxidative stress, according to Gomes *et al.* (79). Aerobic exercise at moderate intensity has been shown to improve exercise performance by minimizing oxidative damage (80). However, shorter-duration, higher-intensity aerobic exercise can significantly increase the risk of oxidative damage; this effect does not reach the DNA level. Exercise type is crucial for oxidative damage: sprinting at the same intensity increases oxidative damage, whereas high-intensity cycling lowers it and boosts anti-oxidant enzymes (81). Due to the ease of implementation and availability of regular exercise as a potential treatment for addiction as well as other psychiatric disorders, it is imperative to identify the appropriate exercise type that produces beneficial effects, along with those that may negatively impact (52).

While physical activity is a potentially beneficial supplementary approach for those with SUD and cognitive deficits, current data do not endorse a uniform exercise regimen for mitigating dementia risk or addressing clinically diagnosed dementia (1, 82). Consequently, exercise must be tailored to the individual, considering the drug type, recovery phase, cognitive condition, physical fitness level, medical comorbidities, psychiatric manifestations, and safety considerations. Present recommendations are to be viewed as practical, evidence-based reflections rather than conclusive therapeutic directives.

Aerobic exercise appears most closely linked to the mechanisms outlined in this review, including cardiorespiratory fitness, cerebral blood flow, mitochondrial adaptability, anti-oxidant defense, neurotrophic signaling, and cognitive performance. Ambulatory activities, stationary cycling, aquatic exercise, and gentle aerobic dance could be viable alternatives, especially for those with limited physical fitness or cognitive impairments (65). Resistance training may confer advantages by increasing muscular strength, promoting functional autonomy, regulating glucose levels, and improving overall health. A synergistic aerobic and resistance regimen may be advantageous, when possible, as it can tackle both cardiorespiratory and functional constraints (81). Nonetheless, empirical data directly comparing aerobic, resistance, and mixed exercise in people with SUD remain scarce. Moderate-intensity exercise could be a pragmatic starting objective, as it is more likely to be accepted and may support beneficial redox and neurological changes. Conversely, vigorous, high-intensity workouts might momentarily elevate oxidative stress, especially in nonathletes or individuals with inadequate nutrition, lack of sleep, or ongoing withdrawal symptoms (83).

Exercise physiology, cognition research, drug-use rehabilitation, and preclinical investigations converge to support these practical aspects. Exercise dose, modality, timing, safety, and clinically diagnosed dementia outcomes in people with SUD, however, have not been thoroughly studied in many trials. Future RCTs should assess adherence and adverse events, compare aerobic, resistance, and combined exercise regimens, and examine whether benefits vary by substance type, age, sex, cognitive state, comorbidities, and recovery stage.

Exercise may help several cognitive, emotional, and oxidative stress-related outcomes in people with SUD, but not all patients will benefit from it. Exercise therapies' viability, safety, and efficacy are probably impacted by several factors, including adherence, the severity of addiction, the stage of recovery, mental and medical comorbidities, pharmaceutical side effects, and substance heterogeneity. Therefore, rather than being a stand-alone intervention, exercise should be viewed as a customized supplement to conventional pharmaceutical and psychosocial treatment (65).

The evidence examined in this study is diverse, including cellular and molecular investigations and animal models. Numerous animal investigations indicate that physical activity may mitigate the neurobiological effects of drug

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Table1. Summary and evidence classification of studies examining substance use, oxidative stress, cognition, and exercise

Study category	Evidence source	Main outcomes	Main interpretation
Cellular/mechanistic	Cell and molecular studies	Reactive oxygen species, mitochondrial dysfunction, antioxidant pathways	Supports biological plausibility
Animal studies	Methamphetamine exposure and voluntary running	Dopaminergic/serotonergic terminal damage	Exercise may reduce drug-related neurotoxicity
Observational human studies	Cohort studies	Substance use and dementia risk	Supports an epidemiological association
Case-control human studies	Methamphetamine users	Oxidative-stress biomarkers	Oxidative imbalance may persist after detoxification
Human intervention study	Methamphetamine-dependent individuals	Cognitive outcomes and malondialdehyde	Suggests possible benefit of aerobic exercise

intake. Voluntary wheel running has been documented to mitigate METH-induced harm to dopaminergic and serotonergic terminals in the striatum. Other preclinical research suggests that both voluntary and enforced physical activity could influence glutamate transmission, striatal mGluR2/3 expression, immediate-early gene activation, neurogenesis, gliogenesis, and hippocampal long-term potentiation. In chronic cerebral hypoperfusion models, treadmill exercise correlates with enhanced cognitive function, augmented hippocampal neurogenesis, and elevated BDNF/pCREB signaling (78–80). Nonetheless, these investigations rely on experimental animal models, and their applicability to cognitive deficits and dementia risk linked with substance use disorders in people remains indirect. Variations in species, exercise regimen, pharmacological exposure, disease model, and result assessment further constrain direct comparison and generalization (81, 84).

However, compared with preclinical research, human exercise data are limited. According to Zhang *et al.*, aerobic exercise was linked to decreases in the lipid peroxidation marker MDA and improvements in specific cognitive outcomes in METH-dependent people. These results are therapeutically significant because they suggest that exercise may affect biomarkers associated with oxidative stress and cognitive function. Nevertheless, the trial did not demonstrate an impact on dementia with a clinical diagnosis, and the data in this evaluation do not provide definitive judgments about randomization, blinding, sample size, control conditions, or long-term follow-up. Therefore, rather than demonstrating that exercise prevents or treats cognitive impairment and dementia risk linked with substance use disorders, the results should be viewed as preliminary evidence for improvements in specific cognitive and biochemical outcomes (39). While some observational studies have connected alcohol use disorder with dementia risk, population-based cohort studies have found a relationship between AMPH-related disorders and an elevated risk of dementia. These results corroborate the epidemiological significance of the link between substance abuse and subsequent cognitive decline. However, a causal relationship cannot be independently established by observational designs. Age, vascular risk factors, educational attainment, psychiatric comorbidity, polysubstance use, socioeconomic status, sleep disturbance, dietary inadequacies, and access to healthcare are examples of potential confounders. Furthermore, the observed relationships may be impacted by misclassification of exposure and diagnosis (85).

Thus, these studies should be interpreted as evidence of increased risk or correlation rather than definitive evidence that substance use directly causes dementia through oxidative stress.

Consequently, molecular insights into ROS, mitochondrial impairment, neuroinflammation, anti-oxidant mechanisms, and synaptic adaptability come primarily from cellular and preclinical studies. Animal studies suggest that physical activity could mitigate drug-induced neurotoxicity, enhance neurogenesis and synaptic plasticity, and influence dopaminergic and glutamatergic transmission. Nonetheless, these results do not directly translate into clinical benefits for dementia. Empirical investigations involving humans have indicated correlations among substance use disorders, oxidative stress, and cognitive deficits; nevertheless, their capacity to determine causation is constrained by possible confounding factors and selection bias. Research involving human subjects is still somewhat restricted and has primarily focused on cognitive abilities or biochemical indicators instead of clinically confirmed dementia (86, 87).

Conversely, the impact of physical activity on oxidative stress is not consistently beneficial and seems to depend on exercise intensity and the physiological environment. Consistent, moderate-intensity physical activity is typically linked to enhanced anti-oxidant capacity and the adaptive stimulation of pathways like Nrf2/ARE. Conversely, intense bouts of aerobic, anaerobic, or resistance training might temporarily increase ROS generation, lipid peroxidation, and several oxidative stress indicators. These results are not inherently conflicting. They may reflect a difference between transient exercise-induced oxidative stress and the prolonged adaptive response to consistent, properly calibrated training. Variations in training status, age, health status, exercise type, duration, intensity, blood-collection timing, and the specific biomarker evaluated may explain the differing outcomes. Significantly, most research has assessed peripheral biomarkers rather than direct indicators of cerebral oxidative stress. Consequently, the ideal exercise dosage for those with substance use disorders and cognitive deficits is still ambiguous and should not be deduced exclusively from preclinical research (39, 88) (Table 1).

Collectively, the available evidence provides a compelling biological rationale for the potential benefits of exercise in mitigating SUD-related cognitive impairments; however,

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the evidence remains insufficient to establish definitive clinical efficacy.

Conclusion

Exercise, as a complementary therapeutic intervention along with other current treatments, may be effective in improving the addiction-induced alterations. Regular exercise may improve cognitive function by increasing dopaminergic activity. Because addicted brains are overexposed to oxidative stress, regular exercise can positively affect brain activity and synaptic plasticity through its anti-oxidant effects, thereby modulating oxidative stress. From this perspective, investigating the exact mechanisms involved in how exercise affects cognitive alternation and dementia caused by addiction can open a new window to overcome symptoms of these diseases, including addiction.

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Authors' Contributions

M F conceived the study and managed the project. F R, F T, and M J wrote the manuscript; M F, F T, and F R reviewed and edited it; and F R and F T conducted the literature review.

Conflicts of Interest

The authors declare no competing interests.

Declaration

We used QuillBot for grammar checking and Gemini 3 to enhance Figure 1 and the graphical abstract.

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