Review

Cognitive Decline in Ageing and Disease: Risk factors, Genetics and Treatments

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ABSTRACT: Aging is the primary risk factor for cognitive decline, impacting multiple cognitive domains and significantly elevating the risk of conditions such as mild cognitive impairment and dementia. In addition to aging, several diseases contribute to cognitive decline. Alzheimer's disease, a progressive neurodegenerative disorder, leads to the loss of neurons and synapses in the brain, resulting in a profound decline in cognitive abilities and functional capacity. Several studies provide compelling evidence that modifiable lifestyle factors play a crucial role in influencing cognitive health. Adopting healthier behaviors has been shown to significantly reduce the risk of cognitive decline. Genetic factors also play a crucial role in cognitive decline, with several genes being identified that influence the risk of developing conditions like Alzheimer's disease and other dementias. Long-term use of opioids and cocaine is also associated with cognitive decline, affecting functions such as memory and executive processes. Understanding the factors contributing to cognitive decline in aging and disease is essential for developing strategies to mitigate its impact. The drugs available to treat patients with cognitive decline due to advanced aging and drug abuse are also summarized.

KEYWORDS: *Ageing, dementia, sleep disorders, drug abuse, cognitive decline, genetics, treatments.*

Introduction

Cognitive decline is a critical issue in both aging and disease, impacting various aspects of mental functioning, including memory, attention, and executive function. As individuals age, they often experience frequently a gradual decline in cognitive abilities, which ultimately can affect their quality of life and independence. This phenomenon is not only a natural part of the aging process but is also exacerbated by various neurodegenerative diseases, most notably Alzheimer's disease and other forms of dementia.

Aging is associated with a range of cognitive changes. Normal aging can lead to mild cognitive decline, characterized by noticeable but not debilitating impairments in memory and other cognitive functions.

However, the progression from MCI to more severe forms of cognitive impairment, such as dementia, is a significant concern for older adults and their caregivers. Dementia encompasses a broad spectrum of cognitive deficits severe enough to hinder with quotidian life, with Alzheimer's disease being the most frequent cause [1].

In addition to aging, several diseases contribute to cognitive decline. Alzheimer's disease, an escalating neurodegenerative disease, leads to neuronal and synaptic loss in the brain, resulting in a profound decline in cognitive abilities and functional capacity [2].

Other conditions, such as Parkinson's disease, Huntington's chorea, and cerebrovascular disorders, also contribute to cognitive deterioration through various pathophysiological mechanisms.

Understanding the factors contributing to cognitive decline in aging and disease is crucial for developing plans of action to lessen its impact. Research has identified several risk factors, including genetic predispositions, lifestyle factors, and comorbid conditions, which can influence the rate and severity of cognitive decline [3].

Early identification and intervention are crucial for managing cognitive decline, with approaches ranging from pharmacological treatments to lifestyle modifications and cognitive training programs.

1. Risk Factors Underlying Cognitive Decline

Cognitive decline, often observed as a decrease in memory, reasoning, and other mental abilities, is a significant concern, particularly in aging populations. This decline can vary in severity, ranging from mild cognitive decline to more severe disorders like dementia and Alzheimer's disease [4].

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10.12865/CHSJ.50.02.02

Understanding the risk factors and genetic predispositions associated with cognitive decline is crucial for developing preventive strategies and therapeutic interventions.

1.1 Cognitive Decline and Old Age

The most significant risk factor for cognitive decline is age. As individuals grow older, the risk of experiencing cognitive impairments increases significantly. The World Health Organization (WHO) emphasizes age to be strongest known risk factor for dementia, including Alzheimer's disease. Dementia prevalence increases significantly with age, affecting 60-70% of individuals over 65 years. This underscores the fact that while aging itself is not a disease, it is the primary risk factor for various forms of cognitive decline and dementia [5].

Indeed, several large and significant clinical studies have established age as the most significant risk factor for cognitive decline. Thus, a comprehensive review highlighted that age-related cognitive decline is a critical issue, often described as the "elephant in the room" due to its vast impact and the aging global population. The authors noted that cognitive functions such as memory, executive function, and processing speed typically decline with age, with the most significant changes occurring in those aged 70 and above [6].

More recently, the "Longitudinal Aging Study Amsterdam (LASA)" that included 2,527 cognitively healthy subjects aged 55-85 years and examined the he link between age and cognitive impairment using various neuropsychological tests such as the Mini-Mental State Examination (MMSE) and the 15 Words Test (15WT), found a significant nonlinear relationship between age and cognitive decline, with older age groups showing more pronounced declines in cognitive function over the follow-up period. The results underscore that cognitive decline accelerates with advancing age, particularly after the age of 70 [7].

In the last decade, researchers have begun looking closely into the Microbiota-Gut-Brain Axis, asking how changes in the gut microbiota with age can influence cognitive functions. As people age, alterations in gut microbiota composition can lead to systemic inflammation and other changes that negatively impact brain health, further supporting the link between aging and cognitive decline [8].

1.2 Cognitive Decline and Cardiovascular Health

Poor cardiovascular condition, including comorbidities like hypertension, diabetes, dyslipidemia, and obesity, is strongly linked to cognitive decline. These conditions can lead to reduced blood flow to the brain, contributing to cognitive impairments. Several large, significant clinical studies support the statement that poor cardiovascular health is strongly linked to cognitive decline.

1.2.1 The Framingham Heart Study (FHS)

This long-term, ongoing cardiovascular cohort study began in 1948 and has since included over 14,000 participants across three generations. The FHS found a significant association between hypertension, diabetes, high cholesterol, and obesity with cognitive decline and dementia. It highlighted how elevated blood pressure and cholesterol levels in midlife are connected to a higher risk of developing Alzheimer's disease as well as other forms of dementia later in life [9].

1.2.2 The Atherosclerosis Risk in Communities (ARIC) Study

This prospective cohort study began in 1987, involving around 15,792 middle-aged males and females from four U.S. communities. The ARIC study found that that patients suffering from hypertension and diabetes had a greater risk of cognitive impairment over a 20-year time span. The study emphasized that these conditions contribute to atherosclerosis, leading to reduced cerebral perfusion and subsequent cognitive impairment [10].

1.2.3 The Cardiovascular Health Study (CHS)

This study started in 1989 and included 5,888 adults aged at least 65 years, from four U.S. communities. The CHS demonstrated that cardiovascular risk factors such as hypertension, diabetes, and high cholesterol levels are linked with a higher risk of cognitive impairment and dementia. The study showed that these conditions lead to vascular changes in the brain, contributing to reduced cognitive function [11].

1.2.4 The Whitehall II Study

This study started in 1985 and included over 10,000 British government officials. The Whitehall II study found that poor cardiovascular health, including hypertension and obesity, is linked to an accelerated decline in cognitive function. It highlighted the role of vascular health in maintaining cognitive abilities during aging [12].

1.3 Cognitive Decline and Lifestyle Factors

A sedentary lifestyle, poor diet, smoking, and exaggerated alcohol consumption are modifiable risk factors that significantly impact cognitive health. Periodical physical activity, a balanced diet high in fruits, vegetables, and essential fatty acids, and avoiding tobacco and exaggerated alcohol may reduce the cognitive decline risk.

1.3.1 The Framingham Heart Study (FHS)

The FHS has shown that sedentarism, poor diet, smoking, and abusive alcohol.

Consumption, are linked with a higher risk of cognitive decline. Conversely, regular physical activity and a balanced diet high in fruits, vegetables, and essential fatty acids are linked with a better cognitive function [13].

1.3.2 Nurses' Health Study (NHS)

This large-scale study has tracked the health of over 120,000 nurses since 1976, examining the impact of lifestyle factors on various health outcomes, including cognitive health. Data from the NHS indicate that smoking, physical inactivity, and bad dietary habits are linked

with higher risks of cognitive decline and Alzheimer's disease. Regular consumption of fruits, vegetables, and omega-3 fatty acids has been linked to better cognitive outcomes [14].

1.3.3 Chicago Health and Aging Project (CHAP)

This community-based study has focused on understanding risk factors for Alzheimer's disease and other dementias in older adults. CHAP has demonstrated that a lifestyle lacking regular physical activity, an unhealthy diet, smoking, and abusive alcohol intake significantly magnified the risk of cognitive impairment. Regular physical activity and a dietary regimen high in fruits, vegetables, and omega-3 essential fatty acids are linked with a reduced risk of cognitive decline [15].

1.3.4 The Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) Study

This study has looked into the impact of cardiovascular risk factors on cognitive health over several decades. The CAIDE study found that modifiable lifestyle factors such as: sedentarism, poor diet, smoking, and abusive alcohol consumption, are linked to a higher risk of dementia. Interventions promoting a healthy lifestyle can help reduce this risk [16].

1.3.5 The Whitehall II Study

This long-term study has followed British civil servants to explore the social determinants of health, including cognitive function. The study has shown that a sedentary lifestyle, smoking, poor diet, and exaggerated alcohol consumption are strongly linked with cognitive decline. Engaging in periodical physical activity and following a healthy diet are protective factors against cognitive deterioration [17].

1.4 Cognitive Decline and Sleep Disorders

Low quality sleep and sleep conditions such as sleep apnea are linked with an increased risk of cognitive impairment. Adequate and quality sleep is crucial for the brain well-being and cognitive function [18].

A comprehensive review and meta-analysis of cohort research papers examined the association between sleep problems and the risk of cognitive degradation or dementia. The analysis, which included over 50 cohorts, found that sleep disturbances and poor sleep quality significantly increase the risk of all-cause cognitive conditions, including Alzheimer's disease and vascular dementia. This large-scale review underscores the critical role of sleep quality in maintaining cognitive function [19].

1.4.1 The Atherosclerosis Risk in Communities (ARIC) Study

This research investigated the link between obstructive sleep apnea (OSA) and cognitive degradation over 15 years in middle-aged to older adults. It found that participants with OSA had a higher rate of cognitive decline compared to those without OSA. This long-term study highlights the impact of sleep-disordered breathing on cognitive health [20].

1.4.2 The BMC Public Health Study

Researchers examined the general population and found that low quality sleep, as quantified by the Pittsburgh Sleep Quality Index (PSQI), was independently linked with low cognitive performance. This study reinforces the idea that sleep quality is a crucial determinant of cognitive health across different populations [21].

2. Cognitive Decline, Old Age, and Genetic Predispositions

Cognitive decline is a significant concern in the aging population, affecting memory, executive function, and overall quality of life. Research into the genetic underpinnings of cognitive decline aims to identify specific genetic markers that can predict susceptibility and provide insights into the biological mechanisms driving this process. This section reviews key genetic markers linked with cognitive decline in

10.12865/CHSJ.50.02.02

aging, highlighting their roles and potential implications for diagnosis and treatment. Genetics also play a crucial role in cognitive decline, with several genes being identified that influence the risk of conditions like Alzheimer's disease and other dementias to develope [22,23,24].

2.1 The APOE Gene

The gene apolipoprotein E (APOE) is one of the most well-studied genetic risk factors for Alzheimer's disease. Individuals possessing the APOE ε4 allele have an increased risk chance of developing Alzheimer's and other dementia types compared to those without this allele [25].

The APOE gene also appears to influence the gut-brain axis, which is crucial for understanding the broader impact of genetic variants on neurodegeneration. This finding underscores the complex interplay between genetics and other physiological systems in the progression of Alzheimer's disease [26].

Recent research has yielded significant insights into the role of the APOE gene in cognitive degradation and Alzheimer's disease. Key findings and developments include:

A recent paper from the Sant Pau Research Institute revealed that nearly all individuals with two alleles of the APOE4 gene (APOE4 homozygotes) develop Alzheimer's pathology by age 55. This includes elevated levels of amyloid and other biomarkers associated with the disease, suggesting that APOE4 homozygosity could be considered a different genetic form of Alzheimer's disease [27].

Researchers at USC also discovered that the APOE4 gene contributes to early breakdowns in the blood-brain barrier, granting harmful substances access in brain areas critical for memory and cognitive functions. This damage often occurs before the appearance of amyloid plaques, indicating potential targets for early intervention in APOE4 carriers [28].

These insights are pivotal for developing personalized prevention and treatment strategies for Alzheimer's disease, particularly for those with a high genetic risk due to APOE4. The ongoing research focuses to refine these strategies and improve early diagnosis and intervention efforts.

2.2 The PSEN1 and PSEN2 Genes

Mutations in genes coding for presenilin-1 (PSEN1) and presenilin-2 (PSEN2) are linked with early-onset familial Alzheimer's disease. Such mutations affect the production of amyloid-beta, a protein associated with the development of Alzheimer's plaques in the encephalon [29].

Recent advancements in the study of the PSEN1 and PSEN2 genes have shed light on their roles in cognitive decline, particularly in the context surrounding Alzheimer's disease (AD). Mutations in these genes are known to contribute to early-onset familial Alzheimer's disease (EOFAD), characterized by progressive cognitive deterioration. Research has identified specific mutations, such as PSEN1 M84V, which increase the synthesis of toxic amyloid-β 42 peptide, thereby accelerating cognitive decline. Additionally, novel PSEN2 mutations, including c.850A>G (p.Arg284Gly), have been discovered, contributing to the understanding of genetic diversity in AD pathology [30,31].

Advanced techniques, such as integrative multiomics and single-cell RNA sequencing, have been pivotal in unraveling the complex genetic interactions in AD. These methods have enabled the identification of common disease endotypes across different mutations in PSEN1, PSEN2, and APP genes, highlighting shared pathways and possible therapeutic targets [32].

This integrative approach is crucial for developing targeted treatments that could modify the disease process rather than just alleviating symptoms. Such research underscores the importance of genetic screening and personalized medicine in managing and potentially mitigating the impact of AD.

2.3 The TREM2 Gene

Variants in the triggering receptor present on the surface of myeloid cells 2 (TREM2) gene are associated with a higher risk of late-onset Alzheimer's disease. TREM2 plays a part in the immune reaction in the brain, and its dysfunction can contribute to neurodegeneration [33,29].

Recent advances in research on the TREM2 gene have provided significant insights into its role in cognitive decline, particularly in relation to Alzheimer's disease (AD). TREM2, a receptor displayed on microglial cells in the brain, is crucial for microglial activation, survival, and response to neuronal damage. Mutations in TREM2, such as R47H, were strongly associated with an increased risk of late-onset AD, impacting microglial lipid metabolism and reducing their ability to respond to beta-amyloid (Aβ) plaques, which are central to AD pathology [34].

New studies have revealed that enhancing TREM2 function can mitigate some neurodegenerative processes. For instance, researchers have shown that increasing TREM2

expression through pharmacological means can reduce myelin damage and potentially ameliorate neurodegenerative symptoms in AD and Parkinson's disease models. Additionally, genome-wide association studies (GWAS) have identified new genetic variants that influence soluble TREM2 (sTREM2) levels in cerebrospinal fluid, further elucidating TREM2's complex role in AD [35].

In vivo models have also demonstrated that TREM2 variants can differentially affect disease progression depending on the stage and type of pathology present. These findings highlight the importance of context when considering TREM2-targeted therapies, suggesting that the therapeutic efficacy of TREM2 modulation may vary with disease severity and specific brain regions affected. Overall, these advancements underscore the therapeutic potential of targeting TREM2 in neurodegenerative diseases and pave the way for new treatment strategies [34].

2.4 Other Genetic Factors

Numerous other genes, including CLU, PICALM, and CR1, have been recognised through genome-wide association studies (GWAS) as contributing to the risk of Alzheimer's disease and cognitive degradation. These genes were associated with various biological processes, including cholesterol metabolic pathway, inflammation, as well as synaptic function [36].

2.4.1 The CLU (Clusterin) Gene

Clusterin (CLU), also known as apolipoprotein J, has been implicated in several neurodegenerative processes. Genetic variants in the CLU gene, particularly the rs11136000 polymorphism, have been linked with higher risk of AD and cognitive impairment. CLU is involved in lipid metabolism, amyloid-beta clearance, and inflammation, making it a critical player in maintaining neuronal health [37].

2.4.2. The CR1 (Complement Receptor 1) Gene

The CR1 gene encodes a protein implied in the clearance of immune complexes and amyloid-beta from the brain. Polymorphisms in CR1, such as rs6656401, have been associated to an increased risk of AD and cognitive decline. The involvement of CR1 in the complement cascade suggests a role for immune system dysregulation in cognitive aging [37].

2.4.3. The PICALM (Phosphatidylinositol Binding Clathrin Assembly Protein) Gene

Variants in the PICALM gene, particularly rs3851179, have been associated with an increased risk of cognitive decline and AD.

PICALM is involved in clathrin-mediated endocytosis, a process critical for synaptic function and amyloid-beta clearance. Disruptions in these pathways may contribute to the accumulation of neurotoxic proteins and synaptic dysfunction observed in cognitive decline [38].

2.4.4. The SORL1 (Sortilin-Related Receptor 1) Gene

The SORL1 gene encodes a sorting protein responsible for trafficking amyloid precursor protein (APP). Variants in SORL1 have been associated with an increased risk of AD and cognitive decline. SORL1 influences the processing of APP, and its dysfunction can lead to a higher production of amyloid-beta, partaking to neurodegeneration [39,23].

2.4.5. The BIN1 (Bridging Integrator 1) Gene

BIN1 is involved in plasmalemmal dynamics as well as and endocytosis, processes essential for neuronal health. Variants in the BIN1 gene, such as rs744373, have been associated with a higher AD risk and cognitive decline. BIN1's role in tau pathology, a key feature of AD, further underscores its significance in cognitive aging [40].

3. Available Treatments for Cognitive Decline in Aging and Disease

Several medications help manage symptoms of cognitive decline, including cholinesterase inhibitors (donepezil, rivastigmine, galantamine), which work by rising levels of acetylcholine in the encephalon, important for memory and learning. Memantine helps regulate glutamate activity to improve cognitive function. Newer monoclonal antibodies (aducanumab, lecanemab, donanemab) target amyloid deposits, associated with Alzheimer's pathology, to slow its progression. However, these drugs may slow the progression of cognitive degradation in Alzheimer's patients but do not cure the disease (Table 1).

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Table 1. Treatment options to slow the cognitive degradation in Alzheimer's Disease patients.

Drug	Brand Name	Mechanism of action	Indication	Side Effects
Donepezil	Aricept	Cholinesterase inhibitor	Mild to moderate Alzheimer's	Nausea, diarrhea, insomnia
Rivaregmine	Exelon	Cholinesterase inhibitor	Mild to moderate Alzheimer's, Parkinson's dementia	Nausea, vomiting, weight loss
Galantamine	Reminyl	Cholinesterase inhibitor	Mild to moderate Alzheimer's	Nausea, vomiting, diarrhea
Mernantine	Namenda	NMDA receptor antagonist	Moderate to severe Alzheimer's	Dizziness, headache, constipation
Aducanumab	Aduhelm	Monoclonal antibody targeting amyloid plaques	Early Alzheimer's	ARIA (amyloid-related imaging abnormalities), headache
Lecanemab	Leqembi	Monoclonal antibody targeting amyloid plaques	Early Alzheimer's	Infusion-related ARIA
Donanemab	Kisunla	Monoclonal antibody targeting amyloid plaques	Early Alzheimer's	ARIA, infusion-related reactions

4. Cognitive Decline and Drug Abuse

Several significant clinical studies have looked into the connection between cognitive decline and drug abuse, highlighting the impact of various substances on cognitive functions.

4.1 General Substance Use Disorders (SUDs)

A review summarized evidence on cognitive impairments associated with various SUDs, indicating that these impairments are prevalent during both addiction, as well as in abstinence phases. These cognitive deficits can significantly hinder addiction treatment outcomes and may persist long after cessation of drug use. Morphological and plastic brain changes due to substance abuse contribute to long-lasting behavioural changes, affecting decision-making, cognition, and emotional regulation [41,42].

4.1.2 Cannabis Use

Research has shown that long-term heavy cannabis use is linked to cognitive impairments, particularly affecting memory and executive functions. These impairments can persist into midlife, raising concerns about the potential increased risk of developing dementia. While some studies suggest a causal relationship, further research is required to look into the full extent of these effects [41].

4.1.3 Alcohol Use

Alcohol use disorders are associated with significant cognitive impairments, including visuospatial memory loss, inhibitory-function issues, and increased impulsivity. These impairments are often stable across various cognitive functions even after a year of sobriety, indicating long-lasting neurological alterations. Conditions like Korsakoff's syndrome, prevalent in individuals with chronic alcohol abuse, exemplify severe cognitive deficits identified by amnesia, executive dysfunction, and social-cognitive impairments [41].

4.1.4 Benzodiazepine Use

A systematic review and meta-analysis investigated the effects of benzodiazepine (BZD) use on cognition in the elderly. The review found that while some studies reported no significant decrease in global cognitive performance, others indicated that BZD users, especially those with higher socioeconomic status or those who abuse BZDs, performed worse on cognitive tests. The impairments were particularly notable in processing speed and memory, as measured by tasks such as the Mini-Mental State Examination (MMSE) and the Stroop Color and Word Test [43].

4.1.5 Opioid and Cocaine Use

Long-term use of opioids and cocaine is also associated with cognitive decline, affecting functions such as memory and executive processes. These impairments can debute after a short period of abstinence and persist over extended periods, potentially up to 12 months. These cognitive deficits highlight the pervasive impact of these substances on brain health and functionality [41,42].

1.2 Genetic pathways underlying cognitive decline in drug abusers

The genetic pathways underlying cognitive decline in drug abusers are multifaceted and involve a complex interplay of neurobiological mechanisms. Chronic drug abuse, particularly of substances such as opioids, cocaine, and methamphetamines, has been shown to induce neurotoxic effects that exacerbate cognitive deficits. These effects are partly mediated by alterations in dopamine signaling pathways, which are crucial for cognitive processes such as learning, memory, and executive function. Genetic polymorphisms in the dopamine receptor

D2 (DRD2) and dopamine transporter (DAT1) genes have been implicated in these cognitive impairments. For instance, individuals with the Taq1A1 allele of the DRD2 gene exhibit reduced receptor availability, leading to diminished dopaminergic function and increased vulnerability to cognitive decline (Noble, 2003).

Additionally, chronic drug exposure can trigger neuroinflammatory responses, involving the activation of microglial cells and astrocytes, which secrete pro-inflammatory cytokines like IL-1β and TNF-α. These cytokines are able to disrupt synaptic plasticity and contribute to neurodegeneration (Crews et al., 2011).

Moreover, genetic variations in the apolipoprotein E (APOE) gene, particularly the ε4 allele, have been linked with a higher risk of cognitive decline in drug abusers. The APOE ε4 allele is known to impair amyloid-β clearance and promote neuroinflammation, further compounding the neurocognitive deficits observed in this population (Levin et al., 2010).

Epigenetic alterations, such as DNA methylation and histone acetylation, also play a critical role in modulating gene expression in response to chronic drug use, thereby influencing cognitive outcomes. For example, hypermethylation of the brain-derived neurotrophic factor (BDNF) gene has been associated with reduced neuroplasticity and cognitive deficits in methamphetamine abusers [44].

Understanding these genetic and epigenetic pathways is essential for developing targeted interventions to mitigate cognitive decline in drug abusers.

Recent research has uncovered significant genetic pathways that contribute to cognitive decline among drug abusers, highlighting complex interactions between genetic and environmental factors. Genome-wide association studies (GWAS) have recognized multiple single-nucleotide polymorphisms (SNPs) linked with increased addiction risk, particularly involving genes that regulate dopamine signalling, which is crucial in addiction and cognitive processes. Notably, variations in these genetic markers not only predispose individuals to substance use disorders (SUDs) but also correlate with higher risks of psychiatric disorders and cognitive decline [45].

One key discovery involves the Nrf2 signalling pathway, known for its role in combating oxidative stress and neurotoxicity. This pathway's dysregulation is implicated in the neurocognitive deficits observed in drug abusers, similar to those seen in chemotherapy-induced cognitive impairment (CICI). Nrf2's activation could potentially mitigate oxidative stress and neuroinflammation, offering a therapeutic target for preventing cognitive decline in these populations [46].

Moreover, genetic studies focusing on mild behavioural impairment (MBI), an early marker of cognitive decline, have revealed associations with specific genetic loci such as APOE and MS4A, which are also linked to Alzheimer's disease (AD). These findings suggest that genetic predispositions to MBI in drug abusers could accelerate the onset of cognitive deficits, driven by mechanisms including neuroinflammation and synaptic dysfunction [47].

The TOMORROW trial has also highlighted the importance of genetic screening for cognitive decline, identifying genes like NCAM2 and ATP6V1E2 that are associated with changes in cognitive functions, particularly in attention. Such insights pave the way for developing targeted interventions to slow or modify the trajectory of cognitive decline in aging and drug-abusing populations [48].

These studies collectively emphasize the profound and often persistent impact of drug abuse on cognitive health, underlining the importance of addressing cognitive impairments in the treatment and management of substance use disorders. A number of drugs are available to treat patients with cognitive decline due to drug abuse (Table 2).

Table 2. Treatment options for patients where cognitive decline is due to drug abuse.

Drug	Class	Mechanism of Action	Reference
Memantine	NMDA Receptor Antagonist	Reduces glutamate excitotoxicity	Pomara, N. et al.[49].
Donepezil	Cholinesterase Inhibitor	Increases acetylcholine levels in the brain	Filley, C. M.[50].
Galantarnine	Cholinesterase Inhibitor	Inhibits acetylcholinesterase and modulates nicotinic acetylcholine receptors	Raskind, M. A., et al. (2008) [51]
Ftivastigmine	Cholinesterase Inhibitor	Inhibits both acetylcholinesterase and butyrylcholinesterase	Winblad,B., et al.(2008)[52].
Bupropion	Norepinephrine-Dopamine Reuptake Inhibitor	Increases norepinephrine and dopamine levels, used for cognitive impairment in methamphetamine users	McGregor, C., et al. (2008) [53].

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Modafinil	Stimulant	Increases dopamine levels and enhances wakefulness and cognitive funtion	Turner, D.C., et al. (2004) [54].
Atomoxetine	Norepinephrine Reuptake Inhibitor	Increases norepinephrine levels, used for attention deficit and cognitive dysfunction	Wilens, T.E. (2006)[55].
Methylphenidate	Stimulant	Increases dopamine and norepinephrine levels, used for cognitive dysfunction in various substance abusers	Levin, F. R., et al. [56].
N-Acetylcysteine (NAC)	Antioxidant	Restores glutathione levels, reduces oxidative stress, and improves cognitive function	Dean, O., et al. (2011)[57].
Omega-3 Fatty Acids	Nutritional Supplement	Anti-inflammatory properties, supports brain health and cognitive function	Sinn, N., & Milte, C. (2010) [58]

Conclusions

In conclusion, cognitive decline is a multifaceted issue influenced by aging and a variety of diseases. Continued research and intervention efforts are necessary to raise the quality of life for those affected and additionally, to develop effective strategies to prevent or slow the progression of cognitive impairment.

These studies underscore that aging is the primary risk factor for cognitive decline, impacting multiple cognitive domains and significantly elevating the risk of conditions such as mild cognitive impairment and dementia with advancing age.

This review also highlights a significant connection between heart health and brain function, indicating that comorbidities, such as high blood pressure, diabetes, elevated cholesterol levels, and obesity may decrease cerebral blood circulation, which in turn can affect mental capabilities.

Understanding the genetic markers associated with cognitive decline in aging provides valuable insights into the mechanisms underlying neurodegeneration and offers potential pathways for early diagnosis and therapeutic intervention.

The identification of these genetic markers paves the way for personalized medicine approaches, where individuals at higher genetic risk can be monitored more closely and potentially benefit from targeted treatments aimed at mitigating cognitive decline.

The available data also underscore the necessity of integrating genetic data with lifestyle and environmental factors to create a comprehensive approach to mitigating cognitive decline in drug abusers.

Future research should focus on diverse cohorts and longitudinal studies to enhance our understanding of these genetic pathways and their interactions with other risk factors.

Overall, these studies provide compelling evidence that modifiable lifestyle factors play a crucial role in influencing cognitive health.

Adopting healthier behaviors has been shown to significantly reduce the risk of cognitive decline.

We also emphasize the profound and often persistent impact of drug abuse on cognitive health, underlining the importance of addressing cognitive impairments in the treatment and management of substance use disorders.

Conflict of interests

None to declare

References

1. Harada CN, Natelson Love MC, Triebel KL. Normal cognitive aging. Clin Geriatr Med, 2013, 29(4):737-752.
2. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med, 2010, 362(4):329-344.
3. Peters R, Booth A, Rockwood K, Peters J, D'Este C, Anstey KJ. Combining modifiable risk factors and risk of dementia: a systematic review and meta-analysis. BMJ Open, 2019, 9(1):e022846.
4. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimaki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbaek G, Teri L, Mukadam N. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet, 2020, 396(10248):413-446.
5. 2024 Alzheimer's disease facts and figures. Alzheimers Dement, 2024, 20(5):3708-3821.
6. Deary IJ, Corley J, Gow AJ, Harris SE, Houlihan LM, Marioni RE, Penke L, Rafnsson SB, Starr JM. Age-associated cognitive decline. Br Med Bull, 2009, 92:135-152.
7. Legdeur N, Heymans MW, Comijs HC, Huisman M, Maier AB, Visser PJ. Age dependency of risk factors for cognitive decline. BMC Geriatr, 2018, 18(1):187.
8. Connell E, Le Gall G, Pontifex MG, Sami S, Cryan JF, Clarke G, Muller M, Vauzour D. Microbial-derived metabolites as a risk factor of age-related cognitive decline and dementia. Mol Neurodegener, 2022, 17(1):43.
9. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med, 2002, 346(7):476-483.

10. Knopman DS, Griswold ME, Lirette ST, Gottesman RF, Kantarci K, Sharrett AR, Jack CR, Jr., Graff-Radford J, Schneider AL, Windham BG, Coker LH, Albert MS, Mosley TH, Jr., Investigators AN. Vascular imaging abnormalities and cognition: mediation by cortical volume in nondemented individuals: atherosclerosis risk in communities-neurocognitive study. Stroke, 2015, 46(2):433-440.
11. Kuller LH, Lopez OL, Mackey RH, Rosano C, Edmundowicz D, Becker JT, Newman AB. Subclinical Cardiovascular Disease and Death, Dementia, and Coronary Heart Disease in Patients 80+ Years. J Am Coll Cardiol, 2016, 67(9):1013-1022.
12. Singh-Manoux A, Kivimaki M, Glymour MM, Elbaz A, Berr C, Ebmeier KP, Ferrie JE, Dugravot A. Timing of onset of cognitive decline: results from Whitehall II prospective cohort study. BMJ, 2012, 344:d7622.
13. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation, 2008, 117(6):743-753.
14. Kang JH, Ascherio A, Grodstein F. Fruit and vegetable consumption and cognitive decline in aging women. Ann Neurol, 2005, 57(5):713-720.
15. Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Associations of vegetable and fruit consumption with age-related cognitive change. Neurology, 2006, 67(8):1370-1376.
16. Kivipelto M, Ngandu T, Fratiglioni L, Viitanen M, Kareholt I, Winblad B, Helkala EL, Tuomilehto J, Soininen H, Nissinen A. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol, 2005, 62(10):1556-1560.
17. Singh-Manoux A, Dugravot A, Shipley M, Brunner EJ, Elbaz A, Sabia S, Kivimaki M. Obesity trajectories and risk of dementia: 28 years of follow-up in the Whitehall II Study. Alzheimers Dement, 2018, 14(2):178-186.
18. Pase MP, Himali JJ, Grima NA, Beiser AS, Satizabal CL, Aparicio HJ, Thomas RJ, Gottlieb DJ, Auerbach SH, Seshadri S. Sleep architecture and the risk of incident dementia in the community. Neurology, 2017, 89(12):1244-1250.
19. Xu W, Tan CC, Zou JJ, Cao XP, Tan L. Sleep problems and risk of all-cause cognitive decline or dementia: an updated systematic review and meta-analysis. J Neurol Neurosurg Psychiatry, 2020, 91(3):236-244.
20. Lutsey PL, Bengtson LG, Punjabi NM, Shahar E, Mosley TH, Gottesman RF, Wruck LM, MacLehose RF, Alonso A. Obstructive Sleep Apnea and 15-Year Cognitive Decline: The Atherosclerosis Risk in Communities (ARIC) Study. Sleep, 2016, 39(2):309-316.
21. Wang Z, Heizhati M, Wang L, Li M, Yang Z, Lin M, Abudereyimu R, Hong J, Yang W, Yao L, Liu S, Hu J, Li N. Poor sleep quality is negatively associated with low cognitive performance in general population independent of self-reported sleep disordered breathing. BMC Public Health, 2022, 22(1):3.
22. Lambert JC, Ibrahim-Verbaas CA, Harold D, Naj AC, Sims R, Bellenguez C, DeStafano AL, Bis JC, Beecham GW, Grenier-Boley B, Russo G, Thorton-Wells TA, Jones N, Smith AV, Chouraki V, Thomas C, Ikram MA, Zelenika D, Vardarajan BN, Kamatani Y, Lin CF, Gerrish A, Schmidt H, Kunkle B, Dunstan ML, Ruiz A, Bihoreau MT, Choi SH, Reitz C, Pasquier F, Cruchaga C, Craig D, Amin N, Berr C, Lopez OL, De Jager PL, Deramecourt V, Johnston JA, Evans D, Lovestone S, Letenneur L, Moron FJ, Rubinsztein DC, Eiriksdottir G, Sleegers K, Goate AM, Fievet N, Huentelman MW, Gill M, Brown K, Kamboh MI, Keller L, Barberger-Gateau P, McGuiness B, Larson EB, Green R, Myers AJ, Dufouil C, Todd S, Wallon D, Love S, Rogaeva E, Gallacher J, St George-Hyslop P, Clarimon J, Lleo A, Bayer A, Tsuang DW, Yu L, Tsolaki M, Bossu P, Spalletta G, Proitsi P, Collinge J, Sorbi S, Sanchez-Garcia F, Fox NC, Hardy J, Deniz Naranjo MC, Bosco P, Clarke R, Brayne C, Galimberti D, Mancuso M, Matthews F, European Alzheimer's Disease I, Genetic, Environmental Risk in Alzheimer's D, Alzheimer's Disease Genetic C, Cohorts for H, Aging Research in Genomic E, Moebus S, Mecocci P, Del Zompo M, Maier W, Hampel H, Pilotto A, Bullido M, Panza F, Caffarra P, Nacmias B, Gilbert JR, Mayhaus M, Lannefelt L, Hakonarson H, Pichler S, Carrasquillo MM, Ingelsson M, Beekly D, Alvarez V, Zou F, Valladares O, Younkin SG, Coto E, Hamilton-Nelson KL, Gu W, Razquin C, Pastor P, Mateo I, Owen MJ, Faber KM, Jonsson PV, Combarros O, O'Donovan MC, Cantwell LB, Soininen H, Blacker D, Mead S, Mosley TH, Jr., Bennett DA, Harris TB, Fratiglioni L, Holmes C, de Bruijn RF, Passmore P, Montine TJ, Bettens K, Rotter JI, Brice A, Morgan K, Foroud TM, Kukull WA, Hannequin D, Powell JF, Nalls MA, Ritchie K, Lunetta KL, Kauwe JS, Boerwinkle E, Riemenschneider M, Boada M, Hiltuenen M, Martin ER, Schmidt R, Rujescu D, Wang LS, Dartigues JF, Mayeux R, Tzourio C, Hofman A, Nothen MM, Graff C, Psaty BM, Jones L, Haines JL, Holmans PA, Lathrop M, Pericak-Vance MA, Launer LJ, Farrer LA, van Duijn CM, Van Broeckhoven C, Moskvina V, Seshadri S, Williams J, Schellenberg GD, Amouyel P. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. Nat Genet, 2013, 45(12):1452-1458.
23. Reitz C, Cheng R, Rogaeva E, Lee JH, Tokuhiro S, Zou F, Bettens K, Sleegers K, Tan EK, Kimura R, Shibata N, Arai H, Kamboh MI, Prince JA, Maier W, Riemenschneider M, Owen M, Harold D, Hollingworth P, Cellini E, Sorbi S, Nacmias B, Takeda M, Pericak-Vance MA, Haines JL, Younkin S, Williams J, van Broeckhoven C, Farrer LA, St George-Hyslop PH, Mayeux R, Genetic, Environmental Risk in Alzheimer Disease C. Meta-analysis of the association between variants in SORL1 and Alzheimer disease. Arch Neurol, 2011, 68(1):99-106.
24. Lourida I, Hannon E, Littlejohns TJ, Langa KM, Hypponen E, Kuzma E, Llewellyn DJ. Association of Lifestyle and Genetic Risk With Incidence of Dementia. JAMA, 2019, 322(5):430-437.

 10.12865/CHSJ.50.02.02

25. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science, 1993, 261(5123):921-923.
26. Seo DO, O'Donnell D, Jain N, Ulrich JD, Herz J, Li Y, Lemieux M, Cheng J, Hu H, Serrano JR, Bao X, Franke E, Karlsson M, Meier M, Deng S, Desai C, Dodiya H, Lelwala-Guruge J, Handley SA, Kipnis J, Sisodia SS, Gordon JI, Holtzman DM. ApoE isoform- and microbiota-dependent progression of neurodegeneration in a mouse model of tauopathy. Science, 2023, 379(6628):eadd1236.
27. Fortea J, Pegueroles J, Alcolea D, Belbin O, Dols-Icardo O, Vaque-Alcazar L, Videla L, Gispert JD, Suarez-Calvet M, Johnson SC, Sperling R, Bejanin A, Lleo A, Montal V. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. Nat Med, 2024, 30(5):1284-1291.
28. Barisano G, Kisler K, Wilkinson B, Nikolakopoulou AM, Sagare AP, Wang Y, Gilliam W, Huuskonen MT, Hung ST, Ichida JK, Gao F, Coba MP, Zlokovic BV. A "multi-omics" analysis of blood-brain barrier and synaptic dysfunction in APOE4 mice. J Exp Med, 2022, 219(11).
29. Luukkainen L, Helisalmi S, Kytovuori L, Ahmasalo R, Solje E, Haapasalo A, Hiltunen M, Remes AM, Kruger J. Mutation Analysis of the Genes Linked to Early Onset Alzheimer's Disease and Frontotemporal Lobar Degeneration. J Alzheimers Dis, 2019, 69(3):775-782.
30. Hsu S, Gordon BA, Hornbeck R, Norton JB, Levitch D, Louden A, Ziegemeier E, Laforce R, Jr., Chhatwal J, Day GS, McDade E, Morris JC, Fagan AM, Benzinger TLS, Goate AM, Cruchaga C, Bateman RJ, Dominantly Inherited Alzheimer N, Karch CM. Discovery and validation of autosomal dominant Alzheimer's disease mutations. Alzheimers Res Ther, 2018, 10(1):67.
31. Lanoiselee HM, Nicolas G, Wallon D, Rovelet-Lecrux A, Lacour M, Rousseau S, Richard AC, Pasquier F, Rollin-Sillaire A, Martinaud O, Quillard-Muraine M, de la Sayette V, Boutoleau-Bretonniere C, Etcharry-Bouyx F, Chauvire V, Sarazin M, le Ber I, Epelbaum S, Jonveaux T, Rouaud O, Ceccaldi M, Felician O, Godefroy O, Formaglio M, Croisile B, Auriacombe S, Chamard L, Vincent JL, Sauvee M, Marelli-Tosi C, Gabelle A, Ozsancak C, Pariente J, Paquet C, Hannequin D, Campion D, collaborators of the CNRMAJp. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med, 2017, 14(3):e1002270.
32. Valdes P, Caldwell AB, Liu Q, Fitzgerald MQ, Ramachandran S, Karch CM, Dominantly Inherited Alzheimer Network, Galasko DR, Yuan SH, Wagner, SL, Subramaniam S. Integrative multiomics reveals common endotypes across PSEN1, PSEN2, and APP mutations in familial Alzheimer's disease. Research Square, 2022, (1-30):10.21203/rs.21203.rs-2356131/v2356131.
33. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Hazrati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J, Alzheimer Genetic Analysis G. TREM2 variants in Alzheimer's disease. N Engl J Med, 2013, 368(2):117-127.
34. Jain N, Holtzman DM. Insights from new in vivo models of TREM2 variants. Mol Neurodegener, 2023, 18(1):21.
35. Wang L, Nykanen NP, Western D, Gorijala P, Timsina J, Li F, Wang Z, Ali M, Yang C, Liu M, Brock W, Marquie M, Boada M, Alvarez I, Aguilar M, Pastor P, Ruiz A, Puerta R, Orellana A, Rutledge J, Oh H, Greicius MD, Le Guen Y, Perrin RJ, Wyss-Coray T, Jefferson A, Hohman TJ, Graff-Radford N, Mori H, Goate A, Levin J, Sung YJ, Cruchaga C. Proteo-genomics of soluble TREM2 in cerebrospinal fluid provides novel insights and identifies novel modulators for Alzheimer's disease. Mol Neurodegener, 2024, 19(1):1.
36. Kok EH, Luoto T, Haikonen S, Goebeler S, Haapasalo H, Karhunen PJ. CLU, CR1 and PICALM genes associate with Alzheimer's-related senile plaques. Alzheimers Res Ther, 2011, 3(2):12.
37. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fievet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, European Alzheimer's Disease Initiative I, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanche H, Dartigues JF, Tzourio C, Gut I, Van Broeckhoven C, Alperovitch A, Lathrop M, Amouyel P. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet, 2009, 41(10):1094-1099.
38. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schurmann B, Heun R, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frolich L, Hampel H, Hull M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Klopp N, Wichmann HE, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet, 2009, 41(10):1088-1093.

39. Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, Katayama T, Baldwin CT, Cheng R, Hasegawa H, Chen F, Shibata N, Lunetta KL, Pardossi-Piquard R, Bohm C, Wakutani Y, Cupples LA, Cuenco KT, Green RC, Pinessi L, Rainero I, Sorbi S, Bruni A, Duara R, Friedland RP, Inzelberg R, Hampe W, Bujo H, Song YQ, Andersen OM, Willnow TE, Graff-Radford N, Petersen RC, Dickson D, Der SD, Fraser PE, Schmitt-Ulms G, Younkin S, Mayeux R, Farrer LA, St George-Hyslop P. The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. Nat Genet, 2007, 39(2):168-177.
40. Naj AC, Schellenberg GD, Alzheimer's Disease Genetics C. Genomic variants, genes, and pathways of Alzheimer's disease: An overview. Am J Med Genet B Neuropsychiatr Genet, 2017, 174(1):5-26.
41. Gasparyan A, Maldonado Sanchez D, Navarrete F, Sion A, Navarro D, Garcia-Gutierrez MS, Rubio Valladolid G, Jurado Barba R, Manzanares J. Cognitive Alterations in Addictive Disorders: A Translational Approach. Biomedicines, 2023, 11(7)
42. Ramey T, Regier PS. Cognitive impairment in substance use disorders. CNS Spectr, 2019, 24(1):102-113.
43. Liu L, Jia L, Jian P, Zhou Y, Zhou J, Wu F, Tang Y. The Effects of Benzodiazepine Use and Abuse on Cognition in the Elders: A Systematic Review and Meta-Analysis of Comparative Studies. Front Psychiatry, 2020, 11:00755.
44. Jiang WX, J.; Lv, R.; Cao, X. Altered levels of blood and brain-derived neurotrophic factor in patients with methamphetamine dependence. Chinese Medical Journal, 2017, 130(10):1171-1175.
45. Hatoum AS, Colbert SMC, Johnson EC, Huggett SB, Deak JD, Pathak G, Jennings MV, Paul SE, Karcher NR, Hansen I, Baranger DAA, Edwards A, Grotzinger A, Substance Use Disorder Working Group of the Psychiatric Genomics C, Tucker-Drob EM, Kranzler HR, Davis LK, Sanchez-Roige S, Polimanti R, Gelernter J, Edenberg HJ, Bogdan R, Agrawal A. Multivariate genome-wide association meta-analysis of over 1 million subjects identifies loci underlying multiple substance use disorders. Nat Ment Health, 2023, 1(3):210-223.
46. Lal R, Dharavath RN, Chopra K. Nrf2 Signaling Pathway: a Potential Therapeutic Target in Combating Oxidative Stress and Neurotoxicity in Chemotherapy-Induced Cognitive Impairment. Mol Neurobiol, 2024, 61(2):593-608.
47. Angelopoulou E, Koros C, Hatzimanolis A, Stefanis L, Scarmeas N, Papageorgiou SG. Exploring the Genetic Landscape of Mild Behavioral Impairment as an Early Marker of Cognitive Decline: An Updated Review Focusing on Alzheimer's Disease. Int J Mol Sci, 2024, 25(5)
48. Mahedy L, Anderson EL, Tilling K, Thornton ZA, Elmore AR, Szalma S, Simen A, Culp M, Zicha S, Harel BT, Davey Smith G, Smith EN, Paternoster L. Investigation of genetic determinants of cognitive change in later life. Transl Psychiatry, 2024, 14(1):31.
49. Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT, Memantine MEMMDSG. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. Curr Alzheimer Res, 2008, 5(1):83-89.
50. Filley CM, Fields RD. White matter and cognition: making the connection. J Neurophysiol, 2016, 116(5):2093-2104.
51. Raskind MA, Peskind ER, Truyen L, Kershaw P, Damaraju CV. The cognitive benefits of galantamine are sustained for at least 36 months: a long-term extension trial. Arch Neurol, 2004, 61(2):252-256.
52. Winblad B, Gauthier S, Scinto L, Feldman H, Wilcock GK, Truyen L, Mayorga AJ, Wang D, Brashear HR, Nye JS, Group G-I-S. Safety and efficacy of galantamine in subjects with mild cognitive impairment. Neurology, 2008, 70(22):2024-2035.
53. McGregor C, Srisurapanont M, Mitchell A, Wickes W, White JM. Symptoms and sleep patterns during inpatient treatment of methamphetamine withdrawal: a comparison of mirtazapine and modafinil with treatment as usual. J Subst Abuse Treat, 2008, 35(3):334-342.
54. Turner DC, Clark L, Dowson J, Robbins TW, Sahakian BJ. Modafinil improves cognition and response inhibition in adult attention-deficit/hyperactivity disorder. Biol Psychiatry, 2004, 55(10):1031-1040.
55. Wilens TE, Kratochvil C, Newcorn JH, Gao H. Do children and adolescents with ADHD respond differently to atomoxetine? J Am Acad Child Adolesc Psychiatry, 2006, 45(2):149-157.
56. Levin FR, Evans SM, Brooks DJ, Kalbag AS, Garawi F, Nunes EV. Treatment of methadone-maintained patients with adult ADHD: double-blind comparison of methylphenidate, bupropion and placebo. Drug Alcohol Depend, 2006, 81(2):137-148.
57. Dean O, Giorlando F, Berk M. N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. J Psychiatry Neurosci, 2011, 36(2):78-86.
58. Sinn N, Milte C, Howe PR. Oiling the brain: a review of randomized controlled trials of omega-3 fatty acids in psychopathology across the lifespan. Nutrients, 2010, 2(2):128-170.

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