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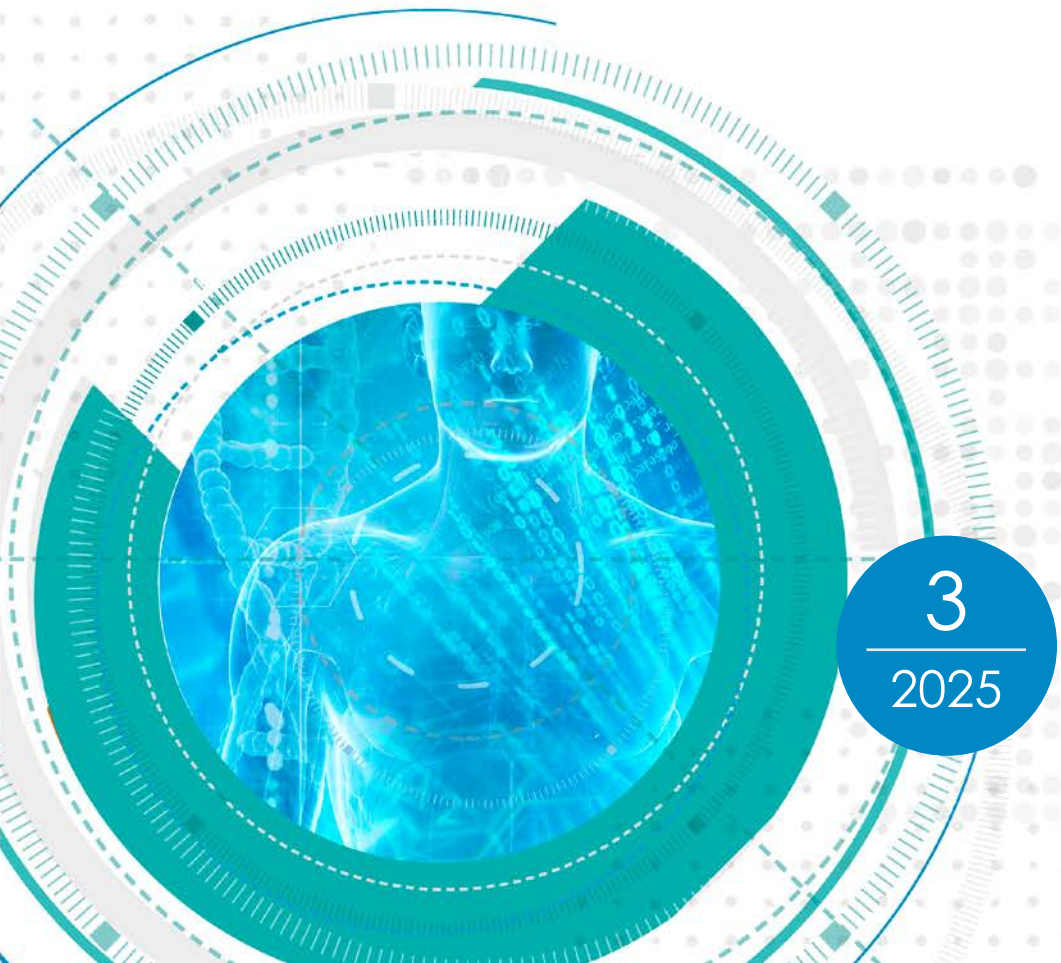

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PREVENTIVE SOFT TISSUE PLASTIC SURGERY IN THE AREA OF THE UPCOMING RECONSTRUCTION OF THE ALVEOLAR BONE OF THE JAWS

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SUMMARY
The article presents a comparative analysis of the results of guided bone regeneration operations using individual titanium skeleton membranes, where in one group, soft tissue plastic surgery was not performed before alveolar bone reconstruction, and in the other group, it was performed accordingly. Soft tissue plastic surgery was performed using the technique of an apically displaced flap with the transfer of a free gingival graft to the wound surface. The individual titanium frame membrane was manufactured using the technology of direct laser sintering of metals on a 3D printer. In patients of the 1st group, 7 cases of complications were registered within a month after the direct bone regeneration (GBR) such as suture divergence and membrane densification. In group 2, after two months, all patients had a keratinized gum attachment with a width of 4–5 mm and a thickness of at least 1.5 mm; then, all patients underwent reconstruction of the alveolar ridge using individually manufactured titanium membranes. In the second group, 1 case of a complication in the form of membrane exposure was registered within a month after the GBR. According to a comparative analysis of the number of complications between the 1st and 2nd groups, statistically significant results were obtained in reducing the number of complications, in the form of suture divergence and membrane exposure, 28 and 4%, respectively, p = 0.049.

KEYWORDS: *targeted bone regeneration, soft tissue plastic surgery, individual titanium membranes, bone plastic surgery.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

ПРЕВЕНТИВНОЕ ПРОВЕДЕНИЕ МЯГКОТКАННОЙ ПЛАСТИКИ В ОБЛАСТИ ПРЕДСТОЯЩЕЙ РЕКОНСТРУКЦИИ АЛЬВЕОЛЯРНОЙ КОСТИ ЧЕЛЮСТЕЙ

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РЕЗЮМЕ
В статье представлен сравнительный анализ результатов проведенных операций по направленной костной регенерации с использованием индивидуальных титановых каркасных мембран, где в одной группе перед реконструкции альвеолярной кости операция мягко-тканной пластики не проводилась, а в другой группе соответственно проводилась. Операции мягко-тканной пластики проводились по методике апикально смещенного лоскута с переносом свободного десневого трансплантата на раневую поверхность. Индивидуальную титановую каркасную мембрану были изготовлены по технологии прямого лазерного спекания металлов на 3D принтере. У пациентов 1-й группы после проведения направленной костной регенерации (НКР) в течении месяца зарегистрировали 7 случаев осложнений, таких как: расхождения швов и оголения мембраны. Во 2-й группе через два месяца у всех пациентов была сформирована кератинизированная прикрепленная десна шириной 4–5 мм и толщиной не менее 1б5 мм; далее всем пациентам была проведена реконструкция альвеолярного гребня с использованием индивидуально изготовленных титановых мембран. Во второй группе после проведения НКР в течении месяца зарегистрировали 1 случай осложнения, в виде оголения мембраны. По проведенному сравнительному анализу по количеству полученных осложнений между 1-й и 2-й группой и получили статистически значимые результаты по снижению количества осложнений, в виде расхождения швов и оголении мембраны, 28 и 4% соответственно p = 0,049.

КЛЮЧЕВЫЕ СЛОВА: направленная костная регенерация, мягко-тканная пластика, индивидуальные титановые мембраны, костнопластические операции

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Relevance

Primary wound healing is one of the key success factors in all bone-grafting operations in the area of the alveolar bone of the jaws. When conducting guided bone regeneration (GBR) in the area of the alveolar bone, the main complication in the postoperative period is the divergence of the sutures and the exposure of the bone grafting area, which subsequently leads to infection of the bone regenerate [1, 2, 3].

In modern studies [5], the above complications are noted quite often — from 15 to 40% of cases.

The results of the study show that with early membrane exposure, the volume of newly formed bone tissue is 5–6 times less than with primary tension healing [4]. To obtain the most predictable result, it is necessary to hermetically suture the flap over the bone regeneration and ensure the stability of the sutures. In the area of bone defects of the alveolar bone, especially in the lower jaw, in addition to bone deficiency, there is also no keratinized gum attachment (KGA). Therefore, mobilized and thinned muco-periosteal flaps often do not provide adequate matching of wound edges and suture retention. As a result of postoperative edema, the sutures erupt and diverge, which leads to the consequences described above. The conducted studies on complications of directed bone regeneration demonstrate that the divergence of the wound edges occurs 2 times more often if the width of the efficiency zone is less than 3 mm [6].

The traditional approach involves soft tissue plastic surgery after bone reconstruction [7].

The purpose of the study was to substantiate the importance of the formation of keratinized attached gums before the upcoming reconstruction of the alveolar bone of the mandible in order to increase the effectiveness of the elimination of defects in the alveolar bone and dental implantation.

Materials and methods

The study was conducted on the basis of the clinical diagnostic center of the Peoples' Friendship University of Russia. The study involved 50 patients (age 36–56) with partial loss of teeth in the lower jaw and atrophy of the alveolar part of the lower jaw in the area of the chewing teeth. Patients of group 1 (25 people) underwent reconstruction of the alveolar part of the lower jaw according to the following protocol: bone grafting using individual titanium skeleton membranes, dental implantation, soft tissue grafting around implants with the formation of keratinized attached gums. In group 2, surgical treatment was performed according to the proposed surgical protocol, namely: before bone grafting, all patients in group 2 underwent soft tissue grafting with the transfer of a free gingival graft to the wound surface to create a keratinized gum. After 2 months, targeted bone regeneration using individual titanium scaffold membranes was performed, and after 6 months, dental implantation was performed. This approach was chosen to reduce the risks of postoperative complications such as suture divergence and infection of the regenerate.

During an intraoral examination of the patients' oral cavity, attention was paid to the color, moisture content of the mucous membrane, and the width of the attached keratinized gum in the area of the intended surgical intervention. The degree of atrophy of the alveolar ridge was assessed, as well as the extent of the defect in the area of missing teeth. At the site of the proposed surgical intervention, the severity of the submucosal layer and the relief of the atrophied alveolar ridge were palpated. Based on the conducted objective studies, the state of oral hygiene and the need for its rehabilitation were assessed.

All patients underwent tests such as a general blood test (RW, HIV, Hbs, blood glucose, clotting). According to the results of the tests, HIV infection, syphilis, markers of hepatitis B, C, acute inflammatory processes in the body were excluded, and special attention was also paid to blood glucose levels. The blood test was also a "marker" for determining the patient's level of health. Based on the data obtained on the patients' health status and the results of blood tests, the relative and absolute contraindications to soft tissue plastic surgery and targeted bone regeneration were determined.

Thus, the studies included patients of health groups I and II, in whom the width of the keratinized attached gum was less than 3 mm in the area of the intended surgical intervention.

In patients of group 1, the reconstruction of the alveolar part of the lower jaw was performed according to a generally accepted protocol, which involves soft tissue plastic surgery after targeted bone regeneration.

At the first stage, patients of group 2 underwent soft tissue plastic surgery in the form of an apically displaced flap and suturing of a free gingival graft (at least 5–6 mm wide) to the wound surface. and the length in accordance with the length of the defect); after 2 months, GBR was performed using an individually manufactured titanium membrane; after 6 months, removal of the individual titanium membrane and dental implantation; After 6 months, gingival cuff shapers were installed and temporary and permanent rational prosthetics on dental implants were performed for 2–3 months.

To demonstrate the need for preliminary soft tissue plastic surgery (STPS) in the field of upcoming bone reconstruction, we provide clinical examples. In the first case, where the STPS was performed before the GBR, the wound was healed by primary tension (Figure 1), and in the second case, where the STPS was not performed after two weeks before the GBR, the necks were exposed (Figure 2).

Fig. 1. Appearance in the oral cavity 2 months after the GBR

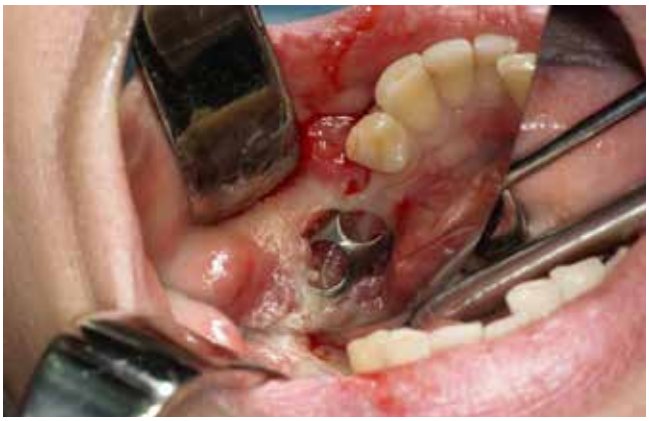

Fig. 2. Appearance in the oral cavity 2 weeks after the GBR

Results and discussion

In patients of the 1st group, 7 cases of complications were registered within a month after the NCR, such as suture divergence and membrane densification. After removal of the individual titanium membranes, the wounds were healed by secondary tension. According to the results of soft tissue plastic surgery in group 2, after two months, keratinized gums with a width of 4–5 mm and a thickness of at least 1.5 mm were formed in all patients; then, all patients underwent reconstruction of the alveolar ridge using an individually manufactured titanium membrane. In the second group, 1 case of a complication in the form of membrane stripping was registered within a month after the NCR. The wound was treated with antiseptic bandages for a month. After monitoring the stability of bone regeneration, the membrane was removed and the wound healed by secondary tension. In other patients from groups 1 and 2, the postoperative (post-NCR) period was the same. Edema in the area of the performed intervention persisted for 3–4 days in the area of the performed intervention. The stitches were removed after two weeks. No complications were detected in the early postoperative and long-term periods (follow-up period up to 4 years). 6 months after the NCR operations, the height and width of the formed bone regenerate were evaluated in all patients according to the results of the CBCT study. In group 1, membrane exposure was n=7 cases, which is 28%. In group 2, membrane exposure was n=1 case, which is 4%. A comparative analysis of the number of complications was performed between the 1st and 2nd groups and statistically significant results were obtained in reducing the number of complications, in the form of suture divergence and membrane exposure, 28% and 4%, respectively, $p = 0.049$. As a result of the comparison of wound healing by primary tension depending on the MTP operation, significant differences were revealed ($p = 0.049$; the method used is the exact Fischer criterion).

Conclusion

Conducting guided bone regeneration operations with a titanium membrane has certain risks of complications of membrane stripping. Thus, our proposed method with the preventive creation of a keratinized gum zone reduces the risks of complications associated with suture failure, exposure and infection of the regenerate.

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NEUROINFLAMMATION AS A CENTRAL LINK IN THE PATHOGENESIS OF NEURODEGENERATIVE DISEASES: MOLECULAR MECHANISMS, CLINICAL CORRELATES, AND THERAPEUTIC PERSPECTIVES

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SUMMARY

Neuroinflammation is regarded as a central mechanism driving the progression of neurodegenerative diseases, integrating age-associated inflammation, glial dysfunction, blood–brain barrier disruption, mitochondrial stress, and systemic factors. Activation of microglia and astrocytes, involvement of the NLRP3 inflammasome, dysregulation of TREM2 signaling, disturbances in iron and lipid metabolism, as well as the influence of the microbiota and metabolic comorbidities together form a self-sustaining pathological network that exacerbates neuronal loss in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Emerging therapeutic strategies include modulation of microglia, inhibition of inflammasome-related cascades, epigenetic approaches, and nanotechnology-based delivery systems for anti-inflammatory compounds; however, their clinical efficacy remains limited. A deeper understanding of the architecture of neuroinflammation opens avenues for the development of targeted and personalized interventions.

KEYWORDS: *neuroinflammation; microglia; NLRP3 inflammasome; TREM2; neurodegeneration; blood–brain barrier.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

НЕЙРОВОСПАЛЕНИЕ КАК ЦЕНТРАЛЬНОЕ ЗВЕНО ПАТОГЕНЕЗА НЕЙРОДЕГЕНЕРАТИВНЫХ ЗАБОЛЕВАНИЙ: МОЛЕКУЛЯРНЫЕ МЕХАНИЗМЫ, КЛИНИЧЕСКИЕ КОРРЕЛЯТЫ И ТЕРАПЕВТИЧЕСКИЕ ПЕРСПЕКТИВЫ

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РЕЗЮМЕ

Нейровоспаление рассматривается как центральный механизм прогрессирования нейродегенеративных заболеваний, интегрирующий возраст-ассоциированное воспаление, глиальную дисфункцию, нарушение гематоэнцефалического барьера, митохондриальный стресс и системные факторы. Активация микроглии и астроцитов, вовлечение NLRP3-инфламмасомы, дисрегуляция TREM2-сигналинга, нарушения железного и липидного обмена, а также влияние микробиоты и метаболических коморбидностей формируют устойчивую патологическую сеть, усиливающую нейрональную утрату при болезни Альцгеймера, болезни Паркинсона, боковом амиотрофическом склерозе и рассеянном склерозе. Появляющиеся терапевтические стратегии включают модуляцию микроглии, подавление инфламмасомных каскадов, эпигенетические подходы и нанотехнологические системы доставки противовоспалительных соединений, однако их клиническая эффективность остается ограниченной. Углубленное понимание структуры нейровоспаления открывает возможности для разработки таргетных и персонализированных вмешательств.

КЛЮЧЕВЫЕ СЛОВА: нейровоспаление; микроглия; NLRP3-инфламмасома; TREM2; нейродегенерация; гематоэнцефалический барьер.

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Introduction

Neurodegenerative diseases (NDDs) represent one of the most significant groups of chronic disorders, characterized by progressive neuronal loss, impairment of synaptic transmission, and a gradual decline in cognitive and motor functions [1]. According to the Global Burden of Disease (2019) analysis, the prevalence of dementia already exceeds 57 million people, and by 2050 it is projected to increase more than two-and-a-half-fold, reaching 152.8 million patients [1]. Another large epidemiological report — GBD 2021 — indicates that disorders of the nervous system have entered the group of leading global causes of disease burden, measured in disability-adjusted life years (DALYs) [2]. Within the spectrum of NDDs, the major contribution is made

by Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and mixed forms of dementia, making neurodegeneration a key challenge for global healthcare [3].

Despite differences in clinical phenotypes, most NDDs share a set of fundamental pathological processes: accumulation of misfolded proteins, mitochondrial dysfunction, disturbed intercellular communication, and progressive chronic inflammation within the central nervous system. For a long time, the pathogenesis of these disorders was considered primarily through the lens of protein aggregates — β-amyloid, hyperphosphorylated tau, and α-synuclein. However, contemporary research convincingly demonstrates that it is sustained neuroinflammation that largely determines the rate of neurodegeneration and influences disease trajectories more substantially than the mere presence of pathological proteins [4].

The core component of this inflammatory response is glial activation. Microglia and astrocytes, responding to protein aggregates as danger-associated molecular patterns (DAMPs), trigger innate immune signaling pathways, including nuclear factor NF-κB and the NLRP3 inflammasome. These processes lead to the release of pro-inflammatory cytokines, disruption of blood–brain barrier (BBB) function, and the formation of a self-sustaining pathological cycle of inflammation and neuronal death [5, 6].

In recent years, the concept of a "neuroimmune connectome" has emerged, reflecting the tight interconnectedness of the central and peripheral immune systems. Numerous studies published in Science and Nature show that neuroinflammation is not confined to local processes within the brain but is closely linked to systemic immune, metabolic, and microbiome-related influences. This substantially broadens our understanding of NDD pathogenesis and underscores the need for an integrative, interdisciplinary approach to their study [7, 8].

The aim of this review is to provide a structured analysis of current data on the cellular and molecular mechanisms of neuroinflammation, its role in the progression of major neurodegenerative diseases, and the therapeutic potential of modulating these processes. Particular attention is paid to the interactions between glial cells, inflammatory signaling pathways, systemic risk factors, and potential therapeutic targets, allowing neuroinflammation to be considered as a central link in the pathogenesis of NDDs and a promising therapeutic direction for the future [4, 7].

Cellular and Molecular Mechanisms of Neuroinflammation

Microglia are the key effector cells of innate immunity in the central nervous system and form the first line of response to structural and metabolic signs of damage. Under physiological conditions, microglial cells maintain homeostasis, perform phagocytosis, monitor synaptic integrity, and participate in trophic regulation. However, under the influence of pathological proteins, mitochondrial stress, metabolic disturbances, or systemic inflammatory signals, microglia transition into activated states characterized by pronounced immune and metabolic changes [9].

Modern models distinguish several functional programs of microglial activation; among them, the conventional M1 and M2 phenotypes are not absolute but remain useful to describe a spectrum of pro-inflammatory and reparative responses. An M1-like state is associated with the production of pro-inflammatory mediators (TNF-α, IL-1β, reactive oxygen species), whereas an M2-like profile is linked to phagocytosis, restoration of the extracellular milieu, and secretion of neurotrophic factors. In chronic neurodegenerative diseases, a persistent shift toward M1-like reactivity is observed, which maintains a long-lasting inflammatory cycle and reduces the compensatory potential of microglia [10].

A central signaling node sustaining this pro-inflammatory response is the NLRP3 inflammasome. Its activation requires two sequential steps: a priming signal that upregulates the expression of inflammasome components, and a subsequent activation signal triggered by cellular stress (disrupted ion homeostasis, mitochondrial ROS, damaged proteins). As a result, caspase-1 is activated and mature IL-1β and IL-18 are released — two key mediators that exacerbate neuroinflammation and neuronal injury. Hyperactivation of the NLRP3 inflammasome has been demonstrated in many neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis [11].

Alongside microglia, astrocytes play an important role in regulating inflammatory processes. These cells respond to cytokines and damage signals by acquiring reactive phenotypes accompanied by metabolic reprogramming, increased secretion of pro-inflammatory mediators, and reduced neurotrophic support. Reactive astrocytes can contribute to synaptic dysfunction, alter neuronal inhibition, and exacerbate brain tissue damage in chronic disease [12]. Under certain conditions, they adopt toxic phenotypes associated with reduced plasticity, impaired glutamate clearance, and potentiation of microglial activation [13].

Neuroinflammation is tightly linked to disruption of the blood–brain barrier. Pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 can alter the expression of endothelial tight junction proteins, increase vascular permeability, and facilitate the infiltration of peripheral immune cells into the brain. This creates a feedback loop: peripheral inflammation exacerbates central inflammation, and central inflammation amplifies systemic immune activation, forming a stable pathological circuit [14]. In addition, microglia directly interact with BBB endothelial cells and pericytes, modulating barrier permeability and participating in the regulation of blood–brain exchange [15].

Recent studies further refine classical concepts of neuroinflammation by incorporating epigenetic and metabolic regulators. For example, m6A modifications of mRNA influence the expression of immune-response genes in microglia and astrocytes, controlling the intensity and duration of inflammatory cascades [16]. Another regulatory node is O-GlcNAc glycosylation, which is sensitive to the energetic and metabolic status of the cell. Alterations in O-GlcNAc levels affect the activity of transcription factors and signaling pathways involved in immune responses and neuronal resilience [17].

Together, these mechanisms form a multicomponent network governing neuroinflammation, involving microglia, astrocytes, BBB endothelium, cytokine signaling, and epigenetic modifications. Persistent dysregulation within this network underlies the transition from a physiological protective response to a chronic inflammatory state that drives the progression of neurodegenerative diseases.

Neuroinflammation in Specific Neurodegenerative Diseases

In Alzheimer's disease, neuroinflammation is considered not a secondary consequence of neurodegeneration but one of the key pathogenic components: β-amyloid and hyperphosphorylated tau trigger sustained microglial activation, formation of specific "disease-associated" microglial phenotypes around amyloid plaques, and maintenance of a chronic pro-inflammatory milieu that promotes progressive synaptic and neuronal loss [18].

Current data show that signaling through TREM2 (triggering receptor expressed on myeloid cells 2) and the NLRP3 inflammasome in microglia constitutes critical nodes through which amyloid aggregates and associated danger signals shift microglia from a phagocytic, relatively neuroprotective state into a chronically activated phenotype, leading to the release of IL-1β, TNF-α, and other mediators that aggravate neuronal damage and cognitive decline in AD [19].

In Parkinson's disease, there is a tight interplay between the accumulation of pathological α-synuclein, mitochondrial dysfunction of dopaminergic neurons in the substantia nigra, and microglial activation, which, via NF-κB and other pro-inflammatory cascades, maintains chronic inflammation and accelerates neuronal death [20].

In addition to protein aggregates, iron deposition in the basal ganglia — especially the substantia nigra — plays a major role in PD. Disrupted iron homeostasis, linked to mitochondrial dysfunction and oxidative stress, promotes the generation of highly reactive oxygen species, microglial activation, and iron-dependent forms of cell death, which correlate with more severe clinical course and motor complications [21].

In amyotrophic lateral sclerosis, pathogenesis is clearly non–cell-autonomous: reactive microglia and astrocytes form complex "disease-associated" states that at early stages may exert neuroprotective effects (trophic support and clearance of damaged structures), but with chronicity shift into neurotoxic phenotypes characterized by dysregulation of glutamate transport, enhanced oxidative stress, and activation of pro-inflammatory pathways that accelerate motor neuron death [22].

Comparative analyses of the pathogenesis of Alzheimer's disease, Parkinson's disease, and multiple sclerosis reveal that in all three disorders persistent involvement of microglia and astrocytes, release of pro-inflammatory cytokines (including IL-1β, IL-6, and TNF-α), and activation of shared signaling pathways (NF-κB, MAPK) create a unified "neuroinflammatory continuum" upon which disease-specific mechanisms are superimposed [23].

In multiple sclerosis, traditionally considered a primarily demyelinating disease, growing evidence indicates that chronic inflammation with microglial activation in the cortex, cortical demyelination, and progressive synaptic loss partially converge with mechanisms of neurodegeneration seen in Alzheimer's disease. This may explain clinical overlaps, cognitive impairment, and the phenomenon of "mixed" dementia forms in a subset of patients [24].

Interplay Between Systemic Inflammation and Neuroinflammation

The gut–brain axis (microbiota–gut–brain axis, MGBA) is considered a key channel linking peripheral inflammatory signals and the immune response of the central nervous system. Disruption of the intestinal microbiota (dysbiosis) alters the production of short-chain fatty acids, microbial metabolites, and endotoxins such as lipopolysaccharide (LPS), leading to activation of innate immunity, shifts in pro- and anti-inflammatory cytokine balance, and increased blood–brain barrier permeability. In turn, this promotes microglial and astrocytic activation, exacerbates neuroinflammation, and accelerates the progression of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Clinical and experimental data indicate that dysbiosis can arise long before the onset of cognitive or motor symptoms, and changes in the microbiome are associated with distinct glial responses and CNS cytokine profiles. In neurodegeneration models, transplantation of "pathogenic" microbiota enhances microglial activation, disrupts astrocyte maturation and function, and increases the accumulation of pathological proteins, whereas normalization of the microbiota partially corrects the neuroinflammatory milieu and attenuates neurodegeneration [25].

Metabolic comorbidities — obesity and type 2 diabetes — generate chronic low-grade systemic inflammation via activation of adipocytes and adipose-tissue macrophages with subsequent release of pro-inflammatory mediators (TNF-α, IL-6, MCP-1, etc.). These signals, together with insulin resistance and oxidative stress, promote glial dysfunction, impair neuronal energy metabolism, drive vascular inflammation, and remodel cerebral microvessels, thereby creating a substrate for cognitive decline and dementia. In experimental models combining Alzheimer's disease and diabetes, astrocytic and microglial alterations have been shown to precede amyloid pathology and exacerbate it, underscoring the leading role of metabolically driven neuroinflammation [26, 27].

Systemic inflammation due to chronic infections, gastrointestinal disorders, and other inflammatory conditions is also associated with more severe courses of neurodegenerative diseases. Meta-analyses and experimental studies demonstrate that peripheral inflammatory stimuli, through circulating cytokines, altered BBB permeability, and endothelial activation, enhance microglial responses, accelerate β-amyloid and pathological tau deposition, and worsen cognitive outcomes. Moreover, several infectious agents (e.g., Helicobacter pylori, herpes simplex virus) are considered modifiable risk factors that, via chronic systemic inflammation and disruption of the gut–brain axis, may intensify the neuroinflammatory component of Alzheimer's disease [28].

These findings show that systemic inflammation — whether metabolic, infectious, or driven by dysbiosis — is not merely a background condition but is actively integrated into the pathogenesis of neurodegeneration via the gut–brain axis and glial–vascular mechanisms, making neuroinflammation a point of convergence for peripheral and central pathological processes.

Mechanisms of Chronic Inflammation and Aging

Chronic low-grade inflammation accompanying aging (inflammaging) is considered one of the key background factors that render the brain vulnerable to neurodegeneration. With age, a persistent dysregulation of innate immunity develops, characterized by elevated levels of pro-inflammatory cytokines, altered microglial and astrocytic phenotypes, disturbed vascular homeostasis, and an increased risk of neurodegenerative diseases. In this context, any additional triggers — from protein aggregates to metabolic and vascular insults — provoke a more pronounced and poorly controlled neuroinflammatory response [4, 26, 27].

Aged microglia lose the capacity for rapid and reversible activation and instead adopt a "primed" phenotype: they maintain a heightened readiness for inflammatory responses, hyperreact to secondary stimuli, and remain in a pro-inflammatory state for longer periods. Age-related microglial changes include accumulation of damaged mitochondria, impaired autophagy, shifts in energy metabolism, and enhanced production of reactive oxygen species (ROS), all of which further reinforce pro-inflammatory programs and lower the activation threshold of the NLRP3 inflammasome. In the presence of amyloid, pathological tau, or α-synuclein, this primed status makes neuroinflammation more persistent and destructive [11, 18–20].

Disturbances in iron and lipid homeostasis become particularly important in the context of aging. In Parkinson's disease, age-associated iron accumulation in the substantia nigra and other basal ganglia structures correlates with increased oxidative stress, microglial activation, and faster progression of motor symptoms. Excess iron participates in Fenton reactions, promoting ROS generation, iron-dependent cell death, and heightened inflammatory responses in glial cells. Likewise, in metabolic comorbidities (obesity, type 2 diabetes), chronic adipose-tissue inflammation and dyslipidemia create a systemic background in which cerebral lipid disturbances (including alterations in neuronal and glial membranes) further contribute to activation of neuroinflammatory cascades [26, 27].

Mitochondrial dysfunction and oxidative stress represent another shared link between aging, systemic inflammation, and neurodegeneration. In neurons and glial cells, age-related declines in mitochondrial efficiency, impaired mitophagy, and increased ROS/RNS (reactive nitrogen species) production lead to accumulation of damaged proteins, lipids, and nucleic acids, which serve as DAMPs for microglia. This closes a vicious circle: mitochondrial stress activates microglia and inflammasomes, while pro-inflammatory cytokines and oxidative stress further deteriorate mitochondrial function, accelerating age-associated neuronal loss [4, 9, 11, 27].

Thus, aging creates a background of chronic, difficult-to-resolve inflammation in which microglial priming, glial dysfunction, iron and lipid dysmetabolism, and mitochondrial stress mutually reinforce one another. These processes are not isolated from systemic metabolic and vascular alterations, but form a unified field of chronic inflammation within which disease-specific pathogenic mechanisms of individual neurodegenerative disorders unfold [4, 9–11, 21, 26–28].

Therapeutic Targets and Strategies

Growing recognition of the role of neuroinflammation in NDD pathogenesis has shifted the focus from purely neuron-centered concepts toward strategies targeting glia, immune cascades, and their molecular regulators. Several classes of promising interventions are currently distinguished: microglia- and inflammasome-targeting agents, antioxidant and anti-inflammatory approaches (including nanotechnology-based formulations and phytocompounds), epigenetic therapies, and biological agents, primarily anti-amyloid monoclonal antibodies.

Microglial activity is considered one of the most straightforward points of intervention in neuroinflammation. Given the established role of the NLRP3 inflammasome in chronic microglial activation in Alzheimer's disease, Parkinson's disease, and other NDDs, small-molecule NLRP3 inhibitors are being explored as candidates to reduce IL-1β and IL-18 production and thereby mitigate neuronal damage in neurodegeneration models. Parallel efforts focus on targeting microglial receptors and "disease-associated" signaling pathways — TREM2, CD33, progranulin (PGRN), TAM receptors, and others — which regulate phagocytosis, microglial metabolism, and survival. The review by Noh et al. emphasizes that TREM2-agonist antibodies (e.g., AL002) and other microglia-targeted interventions are already undergoing clinical evaluation as potential disease-modifying therapies for AD, PD, and ALS, although they remain at early stages of development, with unresolved questions regarding long-term safety and biomarker-based patient stratification [29].

Antioxidant and anti-inflammatory strategies aim to dampen oxidative and cytokine-mediated components of neuroinflammation, with drug delivery across the BBB being a major challenge. In this regard, nanoparticles and nanocapsulated formulations of antioxidants and phytochemicals (curcumin, resveratrol, quercetin, etc.) are being actively developed, improving bioavailability, prolonging action, and potentially enhancing effects on microglia and astrocytes. A systematic review of nano-antioxidants shows that a variety of organic, lipid, and inorganic nanocarriers reduce ROS production, decrease pro-inflammatory cytokine levels, and improve cognitive and behavioral outcomes in preclinical models of Alzheimer's and Parkinson's diseases. Yet almost all data are still limited to in vitro and experimental in vivo studies, underscoring that nanotechnology-based and phyto-neuroprotective approaches currently represent an extended preclinical pipeline rather than ready-to-use clinical tools [30].

Epigenetic modulation of neuroinflammation is another promising direction, particularly in light of the role of m6A RNA modifications and O-GlcNAc glycosylation in regula-

ting immune gene expression. Alterations in the m6A profile in microglia and astrocytes affect the expression of cytokines, innate immune receptors, and signaling molecules involved in Alzheimer's disease pathogenesis, while perturbations in the O-GlcNAc cycle can reshape transcription factor activity and chromatin structure, shifting the balance between pro- and anti-inflammatory programs. Based on these findings, potential therapeutic approaches — inhibitors or activators of m6A-related enzymes (METTL3/14, FTO, etc.) and modifiers of the O-GlcNAc cycle — are being discussed as ways to "reprogram" glial responses. However, as epigenetic reviews stress, any interventions at this level carry a high risk of off-target effects, and at present this field remains largely conceptual and preclinical rather than a source of therapies ready for clinical implementation [16, 17].

Biological agents, primarily anti-amyloid monoclonal antibodies, constitute the first group of approved disease-modifying therapies for early Alzheimer's disease, demonstrating that interventions in pathological protein cascades may indirectly influence neuroinflammation. As highlighted in the review by Koga-Batko et al., aducanumab and donanemab reduce amyloid burden and in clinical trials produce a statistically significant but modest slowing of cognitive decline; their use is associated with amyloid-related imaging abnormalities (ARIA) and requires careful monitoring. Given the close relationship between amyloid pathology, microglial activation, and cytokine dysregulation, these antibodies can be considered indirect modulators of neuroinflammation; however, their effects remain limited, and they do not address the fundamental mechanisms of inflammaging, microglial senescence, and metabolic stress described above [30].

Overall, the therapeutic landscape targeting neuroinflammation currently represents a multilayered system: from direct microglia-focused interventions and nanoparticle-based delivery of antioxidants and phytochemicals to deeper epigenetic strategies and biological agents acting on the amyloid cascade [11, 16, 17, 19, 29, 30]. The key problem is that most of these approaches show convincing benefits only in preclinical models or yield relatively modest clinical effects accompanied by significant risks, which emphasizes the need for more precise patient stratification, rational combination therapies, and integration of biomarkers to monitor neuroinflammation dynamics.

Conclusion

Neuroinflammation is a key integrative link in the pathogenesis of neurodegenerative diseases, connecting genetic predispositions, age-associated changes, immune dysregulation, metabolic disturbances, and vascular factors. Chronic activation of microglia and astrocytes, involvement of inflammasome cascades (primarily NLRP3), blood–brain barrier dysfunction, and interactions with systemic inflammation together form a self-sustaining pathological circuit that drives progressive neuronal damage and synaptic dysfunction.

Despite substantial advances in our understanding of cellular and molecular mechanisms, neuroinflammation remains a complex, multilayered, and heterogeneous process. Different neurodegenerative diseases utilize shared signaling nodes (NF-κB, NLRP3, cytokine networks) but embed them into specific pathogenic patterns — amyloid- and tau-associated inflammation in Alzheimer's disease, α-synucleinopathy and iron-mediated mechanisms in Parkinson's disease, non–cell-autonomous glial responses in ALS, and chronic meningeal and cortical inflammation in multiple sclerosis.

Current therapeutic developments — from microglia-targeted strategies and inflammasome inhibitors to nanotechnology-based platforms and epigenetic interventions — reflect the growing emphasis on precise modulation of inflammatory cascades. However, most of these approaches are still at the preclinical or early clinical stage, demonstrating promising yet limited effects. Approved agents such as anti-amyloid antibodies influence neuroinflammation only indirectly and do not eliminate the fundamental drivers of chronic inflammation.

Future progress will depend on integrating multi-omic biomarkers, developing stratified treatment approaches, modeling disease at the level of cellular networks and microglia–astrocyte interactions, and accounting for systemic factors — microbiota, metabolic disturbances, and chronic infections. Constructing comprehensive models of neuroinflammation will enable the design of more precise and personalized therapeutic strategies capable of truly modifying the course of neurodegenerative diseases.

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NOOTROPICS: EFFECTS ON BRAIN PLASTICITY AND COGNITIVE FUNCTIONS

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SUMMARY

Nootropics represent a heterogeneous group of substances that affect cognitive functions primarily through modulation of neuroplasticity. Classic agents improve neuronal metabolism and, in experimental models, increase neurotrophin levels, but their clinical efficacy in dementia and other cognitive disorders remains moderate. Psychostimulants provide short-term improvement in attention and performance; however, they do not strengthen long-term plasticity and may adversely affect the developing brain. Herbal and nutraceutical agents exert mild and delayed effects, predominantly manifesting in individuals with mild cognitive complaints or deficits. Despite growing interest in pharmacological cognitive enhancement, convincing evidence of a clinically meaningful improvement in cognitive functions in healthy individuals is lacking, whereas the strongest effects on neuroplasticity continue to be demonstrated by non-pharmacological interventions.

KEYWORDS: *neuroplasticity; cognitive enhancement; nootropic drugs; memory; attention; nootropics.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

НООТРОПЫ: ВЛИЯНИЕ НА ПЛАСТИЧНОСТЬ МОЗГА И КОГНИТИВНЫЕ ФУНКЦИИ

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РЕЗЮМЕ

Ноотропы представляют собой разнообразные вещества, влияющие на когнитивные функции преимущественно через модуляцию нейропластичности. Классические препараты улучшают метаболизм нейронов и в экспериментальных моделях повышают уровень нейротрофинов, но их клиническая эффективность при деменции и других когнитивных нарушениях остаётся умеренной. Психостимуляторы дают кратковременное улучшение внимания и работоспособности, однако не усиливают долговременную пластичность и могут неблагоприятно влиять на развивающийся мозг. Растительные и нутрицевтические средства оказывают мягкое и отсроченное действие, преимущественно проявляясь у лиц с легкими когнитивными жалобами или дефицитами. Несмотря на растущий интерес к фармакологическому когнитивному усилению, убедительных данных о значимом улучшении когнитивных функций у здоровых людей нет, а наиболее выраженный эффект на нейропластичность продолжают демонстрировать немедикаментозные вмешательства.

КЛЮЧЕВЫЕ СЛОВА: нейропластичность; когнитивное усиление; ноотропные препараты; память; внимание; ноотропы.

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Introduction

The normal functioning of cognitive processes largely depends on the brain's capacity for neuroplasticity — structural and functional changes in neural networks under the influence of experience and learning. Since the mid-20th century, attempts have been made to pharmacologically improve memory and other cognitive functions. The term "nootropic" was introduced in 1972 by the Romanian chemist C. Giurgea to describe substances that enhance higher brain functions (thinking, learning, memory) without producing stimulation or sedation. Classic nootropics are considered to be pyrrolidone derivatives (piracetam), first synthesized in the 1960s; Giurgea formulated the criteria for a nootropic as follows: enhancement of learning and memory, increased resistance of the brain to damaging influences, and minimal toxicity and side effects. Initially, these drugs were developed forthe treatment of cognitive disorders — dementia, consequences of traumatic brain injury, stroke, and so on.

In recent years, however, there has been an emerging phenomenon of nootropic and stimulant use by healthy individuals (students, knowledge workers) for the purpose of pharmacological cognitive enhancement. Different studies report a wide range of prevalence — from a few to tens of percent — depending on the population and definitions used.

For example, surveys among students have found at least a single use of prescription stimulants (modafinil, methylphenidate, amphetamines) in 1–5% of respondents in European countries, whereas anonymous survey methods show figures up to ~20%. At the same time, the majority — up to 80–90% — of young people do not express interest in such interventions [1–3].

The high demand for "brain improvement" has driven rapid expansion of the market for dietary supplements and products marketed as "smart drugs." More than 100 products are available on online markets, promising to improve memory, attention, creative thinking, and so forth. However, many of them are either poorly studied or fail to demonstrate significant effects under rigorous testing. Ethical issues and concerns about fairness are actively discussed in the context of cognitive enhancement in healthy people. In 2016, the American Medical Association officially opposed prescribing nootropic drugs to healthy individuals because of the uncertain benefit–risk balance.

An integral part of this discussion is the question of how nootropics affect the brain itself — particularly plasticity processes. On the one hand, many nootropics were designed to support neuroplastic changes (restoration of neuronal connections after injury and in dementia). On the other hand, there are concerns that artificially boosting cognitive productivity may come at a "cost" to neuroplasticity — for example, by reducing the natural capacity for adaptive learning or redistributing brain resources. Some reviews have noted that stimulant use at a young age may impair behavioral flexibility and increase vulnerability to addictions by affecting the development of the dopaminergic and glutamatergic systems [4].

The aim of this review is to summarize current scientific data on the effects of different types of nootropic agents on (a) brain plasticity (synaptic and structural) and (b) cognitive functions (memory, attention, executive functions) in humans. The review includes both classic nootropics with predominantly metabolic actions and stimulants and herbal preparations that are frequently referred to as nootropics. We separately consider the proposed mechanisms of action of these agents in the context of neuroplasticity and their actual efficacy according to controlled trials.

Neurobiological mechanisms of nootropics and their effects on brain plasticity

Classic nootropics

The first nootropic, piracetam, was synthesized in 1964 and is still used in a number of countries for the treatment of cognitive impairment. Despite its long history, its exact mechanism of action remains incompletely understood. It is known that piracetam is neither a stimulant nor a sedative and does not exert a direct effect on classical neurotransmitter receptors. Its main actions consist in improving cerebral energy and neurotransmitter metabolism: piracetam and related compounds (aniracetam, oxiracetam, phenylpiracetam, etc.) enhance the utilization of glucose and oxygen by brain tissue, have antihypoxic properties, reduce platelet aggregation, and improve blood rheology in microvessels. Experimental studies have demonstrated increased synthesis of membrane phospholipids and proteins important for synaptic plasticity.

Piracetam has been shown to restore age-related declines in the fluidity of brain cell membrane lipids, which may facilitate receptor function and improve signal transmission. This property is linked to improved neuroplasticity — the ability of neurons to form new connections and maintain long-term potentiation (LTP). In addition, piracetam has demonstrated neuroprotective effects in vitro — it reduces neuronal damage induced by β-amyloid, stimulates mitochondrial function, and attenuates oxidative stress [5].

In animal studies, nootropics frequently enhance molecular markers of plasticity. For example, a combination of Ginkgo biloba and ginseng extracts increased hippocampal levels of synaptophysin and the NR2B subunit of the NMDA receptor — proteins associated with synapse formation. Noopept (a peptide nootropic developed in Russia) acutely increased expression of neurotrophin genes BDNF and NGF in the rat hippocampus. With course administration (28 days), the effect persisted and even intensified, without development of tolerance. This was accompanied by improvements in learning performance and served as a rationale for considering noopept as a promising agent for early-stage Alzheimer's disease prevention. Thus, some classic nootropics can activate intracellular pathways leading to neurotrophic effects and enhanced neuronal plasticity [6].

It should be emphasized that clinical evidence for the efficacy of traditional nootropics is limited. Early small-scale trials often reported improvements in subjective or behavioral measures in patients with cognitive impairment treated with piracetam and other agents. For instance, a meta-analysis of 19 RCTs with piracetam reported a statistically significant global improvement in older adults with dementia or mild cognitive impairment, with a number needed to treat (NNT) of about 7 [7]. However, in those same studies it was not possible to demonstrate consistent benefits on specific neuropsychological tests. Review authors pointed out that the methodological quality of many trials was suboptimal (small samples, missing data from the first phase of crossovers, etc.). A Cochrane Review (2001, updated 2004) concluded that available data do not support the use of piracetam in dementia and that more rigorous trials of ≥6 months are required [8].

Overall, classic nootropics appear to create a favorable metabolic milieu for neuroplastic processes (protecting neurons from hypoxia and damage, improving trophic support and neurotransmitter balance). This may not be sufficient to produce a noticeable cognitive benefit in the absence of concurrent training or rehabilitation, but such agents may potentiate the effects of non-pharmacological interventions, such as cognitive training.

Neuromodulators and stimulants

Another major group of substances used as cognitive enhancers consists of drugs that modulate neurotransmitter levels (primarily monoamines) in the brain. These include psychostimulants: amphetamines (mixed amphetamine salts), methylphenidate, and modafinil. In medical practice, they are

used to treat attention-deficit/hyperactivity disorder (ADHD), narcolepsy, and several other conditions. In healthy individuals, these drugs can indeed produce feelings of wakefulness, enhance concentration, and increase endurance during monotonous tasks.

Their effects on neuroplasticity, however, are ambiguous. On the one hand, transient activation of dopaminergic and noradrenergic pathways improves functional connectivity in attention and executive control networks, translating into better performance in some tasks. For example, a 2010 meta-analysis showed that methylphenidate significantly improves memory (particularly verbal memory) in healthy subjects [9]. Modafinil, in turn, maintains performance, vigilance, and working memory in sleep-deprived volunteers better than placebo. In well-rested individuals, the effect of modafinil is more selective: simple cognitive tests often show no benefit, whereas in complex and novel tasks there may be improvements in attention and executive functions.

At the same time, in most studies stimulants do not enhance creative thinking or cognitive flexibility in healthy individuals; indeed, some reports describe a reduction in divergent thinking under modafinil. A likely explanation is "overloading" of the dopamine–noradrenaline system: excessive focus and hyper-concentration may impair spontaneous associations and strategic flexibility [10].

Long-term psychostimulant use may induce adaptive changes in neural circuits. Animal studies show that chronic methylphenidate administration during the juvenile period disrupts normal maturation of the prefrontal cortex, with reduced behavioral flexibility and a tendency toward more stereotyped learning strategies. Urban and Gao (2014) hypothesized that artificially maintaining high levels of dopamine and glutamate for cognitive enhancement may interfere with normal plastic re-learning processes and increase the risk of addictive behavior [4]. Their review emphasizes that stimulants improve performance on familiar tasks but do not enhance the acquisition of new complex skills and, at high doses or in childhood, may even impair it. In other words, acute cognitive "doping" via stimulation is not equivalent to genuine development of cognitive potential.

From the standpoint of synaptic plasticity, ampakines — experimental nootropics that potentiate AMPA receptor activity — are of particular interest. They directly increase synaptic transmission and, as shown in animal models, can enhance BDNF production in the brain. In a Huntington's disease model, a short course of the ampakine CX929 normalized BDNF levels in the hippocampus, restored actin-dependent structural synaptic changes, and rescued impaired LTP, accompanied by memory improvement in mice [11]. Importantly, these effects were achieved within a few days without major adverse events. Ampakines are considered a promising avenue for activating intrinsic plasticity and memory resources without systemic stimulant effects. None has yet been approved for clinical use, but safety studies are ongoing.

In summary, psychostimulants and neuromodulators exert pronounced short-term effects on neurochemistry that can enhance certain cognitive functions (attention, reaction speed, working memory) in healthy individuals. These effects are confined to an optimal dose range; beyond this, performance worsens according to an inverted U-shaped dose–response relationship. Their contribution to long-term neuroplasticity is doubtful: rather than promoting the formation of new neural connections, they transiently mobilize existing resources. Moreover, concerns remain about potential adverse consequences for plasticity with misuse, particularly at a young age. Clinicians therefore recommend caution with the use of prescription stimulants in healthy individuals, and in children they should be prescribed strictly for ADHD, taking into account the high plasticity of the developing brain and the possibility of long-term consequences.

Herbal nootropics and natural compounds

A substantial share of agents marketed as nootropics consists of natural products (for example, plant extracts). Historically, many medical traditions have used herbs to "calm the nerves" and improve memory. Modern studies of some of these products have shown modest cognitive effects, although the quality of evidence is often limited. The most well-known examples include:

- **Ginkgo biloba.** Standardized Ginkgo biloba leaf extract (EGb 761) is one of the most popular phytotherapeutic agents for memory. Meta-analyses have shown that in patients with dementia, 22–24 weeks of Ginkgo biloba treatment (120–240 mg/day) produce small improvements in cognitive scores and everyday functioning compared with placebo. A 2017 overview noted that Ginkgo may be more effective with long-term use (>5 months) and at doses ≥200 mg. Mechanisms include antioxidant effects, improved cerebral blood flow, and neurotrophic activity — in animal studies, chronic Ginkgo administration increased BDNF levels. Data in healthy individuals are inconsistent: some studies reported slight improvements in processing speed and attention in young volunteers, whereas others found no effect. The effect is probably more pronounced in those with age-related changes. Ginkgo is generally safe but may increase bleeding risk (due to antiplatelet action), so concomitant use with aspirin is undesirable [12].
- **Bacopa monnieri.** An Ayurvedic "brain tonic" traditionally used for fatigue and forgetfulness. Its extracts contain bacosides with antioxidant and neuroprotective properties. Modern RCTs have mostly been conducted in older adults with mild cognitive complaints. A meta-analysis of 9 trials (518 participants) showed that ≥12 weeks of bacopa treatment significantly accelerated information processing (e.g., reduced Trail Making Test-B completion time and choice reaction time). Memory improvements were less consistent, likely due to variability of methods. Some RCTs showed better verbal recall and reduced anxiety with bacopa, but gastrointestinal side effects (nausea, dyspepsia) were more common than with placebo. Overall, bacopa is considered a relatively safe herbal agent with modest nootropic effects upon prolonged use (from 2–3 months), primarily enhancing attention and stress resilience [13].

- **Ginseng (Panax ginseng)**. In traditional Chinese medicine, ginseng is used to "strengthen vital energy," including mental functions. Some studies have shown that a course of Asian ginseng (e.g., 400 mg of G115 extract) can improve working memory and subjective well-being in healthy volunteers. Combined use with Ginkgo (e.g., fixed combinations) improved some cognitive test scores after stroke and in dementia, presumably via synergistic effects on the cholinergic system and neurotrophins. However, large independent studies are lacking, and ginseng's impact on cognitive plasticity remains hypothetical. Ginseng may have a tonic effect (activating the HPA axis and neurotransmitter systems), but specific neuroplastic effects (such as neurogenesis) require confirmation [14].
- **Ashwagandha (Withania somnifera)**. An Indian adaptogen known for its anxiolytic and cortisol-lowering properties. In the cognitive domain, small RCTs have shown that ashwagandha (300–600 mg/day of root extract) improves memory and attention in patients with mild cognitive impairment and in healthy individuals with memory complaints. It is assumed that by reducing anxiety and oxidative stress, ashwagandha creates a more favorable milieu for learning. Experimental studies indicate that it stimulates neurite outgrowth and increases antioxidant enzyme levels in the brain. Ashwagandha is viewed as a promising natural agent, but larger trials are needed [14].
- **Caffeine and other naturally occurring CNS stimulants.** Caffeine is the most widely used psychostimulant and can be considered a situational "nootropic": it acutely increases alertness, reaction speed, and short-term concentration. In combination with L-theanine (an amino acid from tea), caffeine more effectively enhances attention and reduces distractibility than either substance alone. However, these effects are transient, tolerance develops, and high doses cause anxiety and tremor. Theobromine (from cocoa) and nicotine can also transiently improve attention and mood, but because of health risks they are not regarded as acceptable cognitive enhancers. Microdosing of psychedelics (LSD, psilocybin) is currently being discussed as a potential way to enhance creativity and emotional plasticity, as these compounds have been shown to increase neurotrophin levels (BDNF) and synaptogenesis in neuronal cultures. Nonetheless, clinical evidence for cognitive benefits of microdosing is extremely limited, and this approach remains experimental [15].

In general, natural nootropics are characterized by mild effects and a slower onset of action. For instance, a single dose of Ginkgo or bacopa will not immediately improve memory; accumulation and potential neurometabolic shifts over weeks are needed. This contrasts with pharmacologic stimulants (caffeine, amphetamines), whose effects appear within hours. From the perspective of plasticity, it can be assumed that indirect antioxidant and vasotropic actions of herbal nootropics create conditions that support plastic processes — such as protecting neurons from chronic stress and inflammation. Course administration of omega-3 fatty acids and antioxidants, for example, has been associated with higher neurotrophin levels and improved synaptic plasticity in several models of neurodegeneration. In healthy individuals, however, the contribution of nutraceuticals to supranormal cognitive enhancement is minimal. Non-pharmacological factors — such as physical exercise, which robustly increases BDNF and improves memory via hippocampal neurogenesis — have far stronger "nootropic" effects in a healthy brain [16].

Efficacy of nootropics: clinical outcomes and limitations of the evidence

In patients with cognitive impairment

Despite decades of research, no nootropic drug has become a "breakthrough" treatment for dementia or other cognitive disorders. The most effective pharmacotherapeutic strategies in dementia are not classic nootropics but cholinergic agents (cholinesterase inhibitors — donepezil, galantamine) and the partial NMDA antagonist memantine. They provide moderate symptomatic improvement in Alzheimer's disease but their effect diminishes as neurodegeneration progresses.

In the search for adjunctive agents to support cognitive function, classic nootropics have been investigated. Some studies report that combining cholinesterase inhibitors with cholinergic nootropics (e.g., citicoline or alpha-GPC) may yield better cognitive outcomes than cholinesterase inhibitor monotherapy, though data are inconsistent. A 2017 systematic review concluded that in patients with dementia, Ginkgo biloba extract (EGb 761) at 240 mg/day provides cognitive and behavioral improvements comparable to those of cholinesterase inhibitors, and combination therapy may offer additional benefits [17].

In vascular cognitive impairment, piracetam and cerebrolysin (a mixture of neuropeptides) demonstrated small positive effects in some trials, but methodological issues preclude firm recommendations. In post-stroke cognitive dysfunction, cerebrolysin has been assigned level II evidence (probable efficacy) based on several RCTs and a meta-analysis, whereas piracetam did not significantly influence cognitive recovery after stroke [18].

Overall, in clinically overt cognitive impairment, nootropics may provide modest support but do not replace disease-specific therapies. Their effects are most noticeable in mild and early-stage disorders, while they are ineffective in advanced dementia.

In healthy individuals

The question of efficacy in healthy people is particularly controversial. On one hand, widespread self-experimentation with pharmacological enhancers suggests that many individuals subjectively perceive benefits. On the other hand, placebo-controlled trials often show either no effect or very small improvements that do not always reach robust statistical or clinical significance.

For example, a randomized placebo-controlled experiment by Repantis et al. (2021) involving 48 healthy men compared single doses of methylphenidate, modafinil, caffeine, and placebo using a battery of cognitive tests. Only a few improvements were detected: methylphenidate improved delayed recall after 24 hours and reduced subjective fatigue; caffeine enhanced performance in a sustained attention task. Modafinil did not produce significant benefits on any outcome in this sample [19]. At the same time, participants frequently overestimated the degree of improvement under stimulants. This "illusory productivity" effect has been documented for modafinil: subjects reported feeling more productive, although objective measures (except for preventing sleepiness) did not support such impressions. This overestimation may be risky, as individuals may make errors under nootropics due to excessive self-confidence.

Summarizing these data, the most consistent effects in healthy individuals are:

- Stimulants: improve performance under fatigue or sleep deprivation. Modafinil is recognized as an effective countermeasure against cognitive consequences of prolonged wakefulness (e.g., in shift workers or military personnel on extended missions). In well-rested individuals, its benefits are mostly seen in complex tasks requiring integration of multiple cognitive functions. Methylphenidate substantially improves concentration and processing speed, particularly in individuals with lower baseline attention. Caffeine reliably increases alertness and reduces reaction time but does not improve higher-order reasoning or memory for complex structured material.
- Nootropic nutraceuticals: act in the long term. For example, several months of DHA (omega-3) supplementation can enhance attention in young individuals with low baseline omega-3 intake by optimizing membrane processes in neurons. B-vitamins can improve memory performance in the context of deficiency. Nonetheless, in well-nourished healthy people, such supplements do not show effects beyond normalization. Bacopa, after 2–3 months, improves some memory parameters in adults, as demonstrated in several small RCTs (~300 participants in total). Lion's mane mushroom (Hericium erinaceus), which stimulates NGF synthesis, improved cognitive functions in older adults with MCI in a pilot study at 4 g/day for 4 months [20]. All these findings, however, require confirmation in larger trials.

Conclusion

Neuroplasticity — the basis of learning and memory — remains a complex target for pharmacological modulation by nootropics. To date, evidence has accumulated that some nootropic drugs can modulate brain plasticity: classic nootropics (piracetam and analogues) improve cellular metabolism and may increase expression of neuronal growth factors, while experimental agents (ampakines, noopept) can more directly enhance synaptic plasticity via regulation of BDNF and NGF [5, 6, 11, 16]. This supports the possibility of pharmacologic support of cognitive functions in brain injury and neurodegenerative processes. In clinical practice, nootropics have found limited use as part of combination therapy for mild to moderate cognitive impairment, but their effects are generally modest compared with core treatments such as cholinesterase inhibitors [17, 18].

In healthy individuals, nootropic substances do not produce dramatic increases in intelligence. Objective improvements are usually limited to acceleration of simple cognitive operations or increased alertness under specific stress conditions (sleep deprivation, fatigue) [9, 10, 19]. More complex functions — creative thinking, acquisition of new complex skills — are weakly or not at all enhanced pharmacologically; for these, intrinsic plasticity, which cannot be substituted by a "pill," appears to be more important. There is also evidence of potential harm: inappropriate use of stimulants may decrease intrinsic motivation to learn without pharmacologic support, foster psychological dependence, and shift emphasis from long-term skill development to short-term performance. Side effects (insomnia, anxiety, cardiovascular strain) can further negate benefits. Herbal nootropics and nutritional supplements are generally safer, but their efficacy often approximates placebo; exceptions include deficiency states (e.g., vitamins, omega-3), where supplementation restores normal function rather than enhancing it beyond baseline.

At present, there is no "magic pill" that reliably and safely boosts cognitive abilities above baseline in healthy individuals. The most effective strategies for improving memory and brain plasticity remain non-pharmacological interventions — cognitive training, education, physical exercise, and adequate sleep. These factors have strong evidence for increasing neurotrophins (such as BDNF with exercise) and enhancing neural connectivity, providing the foundation for sustained cognitive growth [16]. Pharmacologic nootropics may serve as adjuncts in clinical contexts (post-stroke, after TBI, in early dementia) or in specific short-term situations (night shifts, high-stakes operations), but their use should be carefully evaluated in terms of benefit–risk ratio.

The medical community emphasizes the need for further research: first, on the long-term effects of nootropics on the healthy brain (including developmental processes in youth); and second, on the discovery of new agents that more selectively enhance neuroplasticity without resource depletion. Advances in molecular neurobiology — such as gene therapy and neurotrophic factor — based interventions — may open new horizons for cognitive enhancement in the future. For now, claims about "miraculous" nootropics should be treated with caution: cognitive improvement is a complex, multifactorial process, and pharmacology represents only one of many influences.

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NASAL CONGESTION AND ITS RELATIONSHIP WITH HYPOXIA: PATHOPHYSIOLOGICAL MECHANISMS, CLINICAL CORRELATES, AND THERAPEUTIC PERSPECTIVES

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SUMMARY

Nasal congestion is a common condition in which reduced nasal patency alters respiratory aerodynamics, increases upper airway resistance, and promotes a shift to mouth breathing, particularly during sleep. These changes impair ventilation–perfusion matching, decrease gas-exchange efficiency, and may lead to systemic or local hypoxia, especially in sleep-disordered breathing and in children who are obligate nasal breathers. Clinical evidence demonstrates that both chronic and acute nasal obstruction are associated with reduced SpO_2, increased intermittent hypoxemia, sleep disruption, and cognitive and behavioral consequences. Medical and surgical relief of obstruction improves nasal airflow, decreases the severity of hypoxic episodes, and enhances the effectiveness of sleep-disordered breathing treatment. Thus, maintaining nasal patency is a key component in the prevention and correction of hypoxia across diverse patient populations.

KEYWORDS: *nasal obstruction; nasal congestion; hypoxia; mouth breathing; obstructive sleep apnea.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

ЗАЛОЖЕННОСТЬ НОСА И ЕЕ СВЯЗЬ С ГИПОКСИЕЙ: ПАТОФИЗИОЛОГИЧЕСКИЕ МЕХАНИЗМЫ, КЛИНИЧЕСКИЕ КОРРЕЛЯТЫ И ТЕРАПЕВТИЧЕСКИЕ ПЕРСПЕКТИВЫ

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РЕЗЮМЕ

Заложенность носа – распространенное состояние, при котором снижение носовой проходимости нарушает аэродинамику дыхания, увеличивает сопротивление верхних дыхательных путей и способствует переходу на ротовое дыхание, особенно во сне. Эти изменения ведут к ухудшению вентиляционно-перфузионного соответствия, снижению эффективности газообмена и могут вызывать системную или локальную гипоксию, выраженную особенно при обструктивных нарушениях дыхания во сне и у детей, являющихся облигатными носовыми дыхателями. Клинические данные подтверждают, что как хроническая, так и острая носовая обструкция ассоциированы со снижением SpO_2, усилением интермиттирующей гипоксемии, нарушением сна, когнитивными и поведенческими эффектами. Медикаментозное и хирургическое устранение обструкции улучшает носовое дыхание, снижает выраженность гипоксических эпизодов и повышает эффективность лечения расстройств дыхания во сне. Таким образом, поддержание носовой проходимости является важным компонентом профилактики и коррекции гипоксии у различных категорий пациентов.

КЛЮЧЕВЫЕ СЛОВА: носовая обструкция, заложенность носа, гипоксия, ротовое дыхание, обструктивное апноэ сна.

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Introduction

Nasal congestion — a subjective sensation of "blocked" nasal passages with reduced airflow — is among the most frequent complaints that lead patients to seek care from otorhinolaryngologists and primary care physicians. It accompanies a wide range of conditions, from acute viral rhinitis to chronic allergic rhinitis and chronic rhinosinusitis with nasal polyps. Allergic rhinitis alone affects approximately 25% of the global population, and nasal congestion is often its most burdensome symptom. In addition to discomfort and reduced quality of life (e.g., impaired sleep and daytime performance), there is increasing awareness of the potential

systemic physiological consequences of nasal obstruction. In particular, there is justified concern that pronounced nasal congestion may reduce oxygen intake and cause tissue hypoxia in several clinical scenarios [1].

Hypoxia, defined as insufficient oxygen delivery to tissues, is a key pathophysiological factor in many diseases and may arise as a consequence of impaired breathing. Obstructive sleep apnea (OSA) illustrates how elevated upper airway resistance and airway collapse produce intermittent nocturnal hypoxemia, contributing to cardiovascular and cognitive comorbidities. Nasal obstruction is a modifiable factor that can exacerbate OSA severity in many patients. Epidemiological data show that habitual nighttime nasal congestion is associated with higher rates of snoring and OSA. In a population-based cohort study, individuals with persistent severe nighttime congestion had approximately a threefold higher likelihood of habitual snoring compared with those without congestion. OSA itself is highly prevalent (approximately 1 billion people worldwide), and its hallmark — recurrent hypoxemia — underlies many of its systemic consequences [2].

The purpose of this review is to analyze the relationship between nasal congestion and hypoxia. We examine the mechanisms through which nasal obstruction can reduce oxygenation — both systemically (hypoxemia) and locally (mucosal hypoxia) — along with clinical contexts in which this association is most significant. Particular attention is paid to the impact of nasal versus oral breathing on gas exchange, the role of nasal congestion in sleep-disordered breathing and intermittent hypoxia, the vulnerability of infants and children who rely on nasal respiration, and the potential benefits of relieving nasal obstruction for hypoxia-related outcomes. Synthesizing current evidence may help clinicians view nasal congestion not only as a local symptom but also as a factor with broader physiological implications.

Physiology of Nasal Breathing and Oxygenation

Under normal circumstances, humans predominantly breathe through the nose, and nasal airflow serves several essential physiological functions. The nasal passages warm, humidify, and filter inspired air, and they are a major source of nitric oxide (NO) produced in the paranasal sinuses. NO enters the lower airways during nasal inhalation and acts as an "aerocrine" mediator that enhances pulmonary oxygen uptake and reduces pulmonary vascular resistance. Experimental studies demonstrate that nasal breathing improves arterial oxygenation compared with oral breathing. Lundberg et al. showed that in healthy adults, transcutaneous oxygen tension ($tcPO_2$) was approximately 10% higher during nasal breathing, likely due to inhalation of endogenous NO and more favorable airflow distribution. In mechanically ventilated patients deprived of nasal airflow, reintroduction of NO-rich nasal air increased arterial oxygen tension (PaO_2) by 18% and reduced pulmonary vascular resistance by 11%, underscoring the direct contribution of nasal-derived NO to gas-exchange efficiency [3].

A second important aspect is airway resistance. While the nasal airway creates resistance, it supports physiologically optimal airflow patterns. During wakefulness, the difference in resistance between nasal and oral breathing may be modest, but the difference becomes pronounced during sleep. In the classical study by Fitzpatrick et al., healthy volunteers were evaluated during sleep under forced oral versus nasal breathing. Oral breathing produced substantially higher upper airway resistance (median ~12.4 cm $H_2O \cdot L^{-1} \cdot s^{-1}$) compared with nasal breathing (~5.2 cm $H_2O \cdot L^{-1} \cdot s^{-1}$) during stage 2 sleep. The greater collapsibility of the oropharynx with an open mouth accounted for most of this difference. The apnea–hypopnea index (AHI) was almost negligible during nasal breathing (~1.5 events/h) but reached pathological values during forced oral breathing (~43 events/h). This clearly demonstrated the mechanical advantage of nasal breathing in maintaining upper airway stability during sleep. Nasal breathing promotes physiologic jaw and tongue positioning (tongue against the palate), whereas mouth breathing causes posterior displacement of the tongue and airway narrowing. Thus, adequate nasal patency is crucial for stable nocturnal respiration without episodes of apnea and hypopnea [4].

In summary, the nasal passages play a central role in respiratory physiology by improving oxygenation (via NO-mediated effects on pulmonary hemodynamics) and stabilizing the upper airway. When nasal breathing is impaired, these advantages are lost. The next sections discuss how nasal congestion — by inducing mouth breathing or increasing resistance — can lead to measurable reductions in oxygenation.

Effects of Nasal Obstruction on Oxygenation and Breathing

Severe nasal obstruction (pronounced congestion or complete blockage) disrupts normal breathing mechanics. A frequent and immediate consequence is a shift to mouth breathing, which, as noted above, reduces ventilation efficiency and upper airway stability during sleep. Additionally, nasal obstruction may alter breathing parameters during wakefulness. Increased total airway resistance elevates the work of breathing, promoting hypoventilation: breathing becomes more shallow and less effective. As a result, blood oxygen levels (hypoxemia) may decrease, and $PaCO_2$ may rise (hypercapnia) if minute ventilation cannot be adequately maintained [5].

Clinical studies demonstrate the effect of acute and chronic nasal obstruction on gas exchange. In patients with long-standing nasal obstruction (septal deviation, polyposis, turbinate hypertrophy), baseline PaO_2 may be moderately reduced ("latent" hypoxemia) even in the absence of pulmonary disease. Sobh et al. evaluated 59 adults undergoing surgery for nasal obstruction (mostly septoplasty or polypectomy) and assessed arterial blood gases before and after surgery. Preoperatively, some patients exhibited low-normal PaO_2 and SpO_2. When postoperative nasal packing completely blocked nasal airflow, PaO_2 and SpO_2 decreased further, accompanied by a mild drop in pH (suggesting slight hypercapnia). After removal of the nasal packing (restored nasal breathing), oxygenation improved and exceeded preoperative levels. This reversible experiment directly demonstrates that nasal obstruction can induce hypoxemia, likely through hypoventilation and ventilation–perfusion mismatch.

Earlier studies reported similar findings. Öğretmenoğlu et al. showed that bilateral nasal packing in postoperative patients significantly reduced nocturnal oxygen saturation, whereas nasal airway tubes mitigated desaturation. Cassisi et al. (1971) showed that posterior nasal packing for epistaxis

significantly decreased PaO_2 in adults, with minimal changes in $PaCO_2$; hypoxemia resolved after removal of packing. Proposed mechanisms include reflex pathways (e.g., the "nasopulmonary reflex," reducing respiratory drive) and mechanical factors (mouth breathing with increased pharyngeal collapsibility). The resulting cascade is: nasal blockage → mouth breathing + reflex hypoventilation → ventilation–perfusion mismatch → hypoxemia [6, 7].

Local mucosal hypoxia of the nasal and sinus tissues is also significant. When sinus ventilation is impaired (as in chronic rhinosinusitis with polyps), oxygen tension in the sinus cavities decreases. Such hypoxia promotes inflammation by stabilizing hypoxia-inducible factor-1α (HIF-1α) and upregulating pro-inflammatory gene expression. The review by Zhong et al. (2022) highlights that hypoxic conditions in chronically inflamed sinonasal mucosa worsen epithelial dysfunction and polyp growth, creating a vicious cycle: obstruction → hypoxia → inflammation → further obstruction [8].

Individual variability should be noted. In a small study by Taasan et al., healthy volunteers underwent complete nasal occlusion during sleep assessment. Despite severe discomfort and forced oral breathing, some subjects did not exhibit significant desaturations. The authors suggested that young healthy adults can compensate effectively over short periods via oral breathing, and the small sample size (N=7) limits generalizability. Thus, short-term nasal obstruction in healthy subjects may be well tolerated, whereas patients with comorbidities or prolonged sleep are more prone to developing hypoxemia. Overall, the available evidence indicates that pronounced bilateral nasal obstruction adversely affects oxygenation, particularly during sleep or sedation, when compensatory mechanisms are diminished [9].

Nasal Congestion in Sleep-Disordered Breathing and Intermittent Hypoxia

The strongest link between nasal congestion and hypoxia is observed in sleep-disordered breathing — snoring and OSA. During sleep, muscle relaxation and the supine position predispose the airway to collapse; increased nasal resistance due to congestion further exacerbates this risk by promoting mouth breathing and upper airway instability.

Epidemiological and clinical studies confirm the association between reduced nasal patency and OSA. In the Wisconsin Sleep Cohort, individuals with chronic nighttime nasal congestion ("often" or "always") had a significantly higher risk of habitual snoring and probable undiagnosed OSA. A longitudinal analysis showed that subjects with severe nighttime congestion were nearly three times more likely to develop habitual snoring over five years. Allergic rhinitis — a common cause of chronic congestion — is associated with at least a twofold increase in OSA risk, primarily due to increased nasal resistance and mouth breathing during sleep. Chirakalwasan et al. showed that effective treatment of allergic rhinitis can moderately reduce OSA severity, underscoring the contributory role of nasal obstruction [10–12].

The mechanistic link is clear: nasal obstruction increases airway resistance and forces mouth breathing, which — as shown earlier — substantially increases the risk of obstructive events. Additionally, nasal obstruction reduces afferent stimulation from nasal airflow receptors that help maintain respiratory drive, potentially lowering ventilation during sleep transitions. Experiments with artificial nasal occlusion provide compelling evidence. Metes et al. demonstrated that nasal occlusion in healthy individuals induced snoring and apnea that were not present during normal nasal breathing. In patients with OSA, Lan et al. (2021) found that those with narrower or more resistant nasal passages spent more time in nocturnal hypoxemia, concluding that nasal obstruction is an "important factor" contributing to hypoxemia in moderate-to-severe OSA [11].

Intermittent hypoxia drives sympathetic activation, oxidative stress, inflammation, hypertension, cardiovascular disease, and cognitive decline. A newer metric — the hypoxic burden (area under the curve of oxygen desaturations during sleep) — has been shown to be a stronger predictor of cognitive impairment and cardiovascular outcomes than AHI alone. Huang et al. demonstrated that in OSA patients, higher hypoxic burden was associated with a significantly greater risk of mild cognitive impairment at comparable AHI values. This suggests that any factor worsening desaturation (including nasal congestion) may accelerate cognitive decline [13–16].

Improving nasal airflow can reduce OSA severity or improve disease control. Randomized trials show that intranasal corticosteroids in allergic rhinitis patients with OSA reduce AHI by 30–40% and improve subjective sleep quality and daytime alertness. Nasal surgery (septoplasty, turbinate reduction, polypectomy) often improves CPAP tolerance and may decrease apnea frequency in selected patients. Although nasal surgery rarely cures OSA, it provides clinically meaningful benefits, especially by improving CPAP adherence. McNicholas emphasized that variable obstruction (such as nighttime congestion or positional effects) may play a more important role in OSA physiology than fixed anatomical narrowing [13–16].

Oxidative stress is also relevant. Passali et al. (2025) reported elevated oxidative stress biomarkers in patients with isolated nasal obstruction (AHI <5) at levels comparable to those in OSA patients. This indicates that impaired nasal airflow alone may initiate systemic oxidative–inflammatory responses, supporting a continuum: isolated obstruction → snoring → OSA, united by hypoxia–reoxygenation cycles [15].

Thus, nasal congestion is both a risk factor for sleep-related hypoxemia and an exacerbating component in established OSA. Patients with chronic congestion and sleep symptoms should be evaluated for sleep-disordered breathing, and nasal pathology should be considered a treatment target to improve oxygenation, cognitive function, daytime alertness, and cardiovascular outcomes.

Special Populations: Pediatric Patients and the Impact of Nasal Obstruction

Infants and young children

Infants are particularly vulnerable to the consequences of nasal congestion. Newborns are predominantly nasal breathers in the first months of life. Due to anatomical and reflex factors, they have limited ability to switch effectively to oral breathing, especially during feeding. Even moderate

nasal obstruction can lead to respiratory distress, feeding difficulties, and hypoxic episodes. Trabalon and Schaal showed that forced oral breathing due to nasal obstruction significantly affects neonatal systemic adaptation and behavior. The clinical relevance is evident in bilateral choanal atresia — a congenital blockage of the posterior nasal airway. Affected infants are cyanotic and hypoxic at rest but improve during crying (temporary oral airflow), highlighting the critical role of nasal breathing for oxygenation in early life. Even less severe congestion (e.g., neonatal rhinitis or residual milk in the nasopharynx) may cause desaturation or apnea. Therefore, nasal hygiene (saline irrigation and secretion removal) is routinely recommended to prevent respiratory and hypoxic episodes in infants. Maintaining nasal patency during this period is essential to prevent hypoxemia and its consequences, including inadequate weight gain, impaired growth, and a theoretical contribution to sudden infant death risk in extreme cases [17].

Older children and adolescents

In preschool and school-aged children, chronic nasal obstruction is most commonly due to adenoid hypertrophy and/or allergic rhinitis. Such children often become chronic mouth breathers. Mouth breathing in childhood is associated with craniofacial abnormalities (long face, high-arched palate), sleep disturbances, and cognitive and behavioral impairments. Pediatric sleep-disordered breathing (often due to adenotonsillar hypertrophy) leads to intermittent hypoxia that adversely affects neurocognitive development and growth hormone secretion. Untreated pediatric OSA is associated with deficits in memory, attention, academic performance, and behavioral issues resembling ADHD. Even milder forms — primary snoring with mouth breathing — can negatively affect daytime function. In a cross-sectional study by Kuroishi et al., children with "mouth breathing syndrome" performed significantly worse on tests of working memory, reading comprehension, and arithmetic skills compared with nasal breathers [18].

Nocturnal hypoxemia is common in mouth-breathing children, even without full OSA. Allergic inflammation further disrupts sleep architecture. Parents frequently report snoring, noisy breathing, daytime sleepiness, and inattention. Many symptoms improve after adenotonsillectomy or effective allergy treatment [19].

Growth is another important aspect. Chronic hypoxemia from sleep-disordered breathing may suppress nocturnal growth hormone secretion. "Catch-up" growth is frequently observed after adenotonsillectomy. Similarly, restoring nasal patency may support adequate oxygenation required for optimal growth. Some observational studies show that treating allergic rhinitis improves not only sleep but also weight gain and growth metrics in children, likely by reducing breathing effort and hypoxic stress during sleep.

In adolescents, mouth breathing may persist and contribute to reduced tongue strength, impaired oral function, and lower cognitive performance. Masutomi et al. (2024) showed that adolescents who mouth breathe have reduced oral musculature performance and poorer cognitive scores compared with nasal breathers. Residual snoring or mild OSA is often present. Restoring nasal airflow — medically or orthodontically — remains important even at this age [19].

Thus, pediatric populations vividly demonstrate that nasal congestion can lead to hypoxia-associated problems, from acute respiratory compromise in infants to cognitive and growth impairments in older children. Early identification and treatment of nasal obstruction (medical, surgical, orthodontic) are essential to prevent these adverse outcomes.

Therapeutic Perspectives: Reducing Hypoxia by Relieving Nasal Obstruction

Given the evidence that nasal congestion contributes to hypoxemia and reduces ventilation efficiency, it is reasonable to assume that correcting obstruction may provide benefits beyond symptom relief — improving oxygenation and clinical outcomes. Therapeutic approaches include medical and surgical treatments, often combined.

Medical therapy targets reversible causes of congestion. In allergic rhinitis, intranasal corticosteroids are first-line agents; they reduce mucosal inflammation and edema. Improved nasal airway patency decreases mouth breathing and snoring. As noted above, randomized trials in children and adults with combined allergic rhinitis and OSA have shown that intranasal steroids produce moderate reductions in AHI and significant improvements in sleep quality and daytime alertness. Adjunctive therapies include antihistamines (for allergy), anticholinergic nasal sprays (for vasomotor rhinitis), and isotonic saline irrigations. Short-acting topical decongestants (oxymetazoline and others) provide rapid relief in acute rhinitis or during CPAP titration in congested patients but are limited by the risk of rhinitis medicamentosa. In OSA patients with pronounced nasal congestion, combining intranasal steroids with a decongestant improves CPAP tolerance and adherence — an important practical consideration, as optimizing nasal airflow helps disrupt the cycle of "nasal obstruction → CPAP intolerance → persistent hypoxia" [20].

Surgical interventions are indicated in structural abnormalities and chronic rhinosinusitis unresponsive to medical therapy. Septoplasty (often with turbinate reduction) significantly improves nasal airflow. Several studies report improvements in pulmonary function and oxygenation in patients with preexisting nasal obstruction following septoplasty. In one observational study, patients with septal deviation and snoring experienced improved minimum nocturnal oxygen saturation and reduced apnea frequency one month postoperatively. Endoscopic sinus surgery and polypectomy also relieve congestion and reduce local hypoxic inflammatory stimuli. Although nasal surgery alone rarely cures OSA, some patients — particularly those with mild disease where nasal obstruction is the major contributor — achieve clinically significant improvements. Most patients benefit indirectly through improved CPAP adherence.

New devices and technologies reflect the importance of nasal airflow. Nasal expiratory positive airway pressure (EPAP) devices are used for snoring and mild OSA and rely on nasal patency to generate positive pressure on exhalation. Their efficacy depends directly on unobstructed nasal passag-

es. High-flow nasal oxygen therapy, widely used in hospitals, also requires preserved nasal flow and can prevent hypoxemia in partial upper airway obstruction [20].

From a preventive standpoint, especially in pediatrics, early treatment of allergic rhinitis and timely adenoidectomy (when indicated) prevent long-term consequences of chronic hypoxia. Orthodontic interventions (e.g., rapid maxillary expansion) are used in children with high-arched palates and nasal narrowing to increase nasal cavity volume, which may improve nocturnal breathing and oxygenation.

Thus, targeted correction of nasal congestion should be considered part of the therapeutic strategy for patients with hypoxemia or sleep-disordered breathing secondary to nasal obstruction. In OSA, clinicians should maintain a low threshold for active nasal treatment: simple measures (daily intranasal steroids, allergen control) can reduce apnea frequency and increase minimum saturation levels. For structural obstruction, timely surgical correction is indicated — not only for subjective comfort, but also to reduce the contribution to systemic hypoxia. Relieving nasal congestion may improve cognitive function, daytime alertness, and blood pressure control by reducing intermittent hypoxia and sympathetic activation.

Conclusion

Nasal congestion and hypoxia are closely interconnected: reduced nasal patency increases airway resistance, promotes mouth breathing, and raises the likelihood of upper airway collapse during sleep, leading to intermittent hypoxia, sympathetic activation, and oxidative stress. Infants and children are especially vulnerable, as even moderate obstruction may cause desaturation, sleep disruption, cognitive impairment, and growth disturbances. Clinical evidence shows that medical and surgical correction of nasal obstruction improves oxygenation, reduces apnea frequency, and enhances sleep quality, although the effect depends on the severity of obstruction, anatomical factors, and comorbid conditions. Gaps remain in defining threshold levels of nasal resistance that produce clinically significant hypoxia and in evaluating the long-term impact of treating chronic nasal congestion on OSA risk and cardiovascular outcomes.

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ПАТОФИЗИОЛОГИЯ ОБСТРУКТИВНОГО АПНОЭ СНА

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SUMMARY

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by recurrent episodes of upper airway obstruction leading to apnea and hypopnea. A combination of anatomical and functional factors contributes to the development of OSA: narrowing of the upper airway (e.g., due to obesity or craniofacial features), reduced tone of pharyngeal dilator muscles during sleep, increased ventilatory drive (ventilatory control instability, high loop gain), and a low arousal threshold. These factors promote pharyngeal collapse during sleep with episodes of hypoxia and arousals. Recurrent intermittent hypoxia and sleep fragmentation trigger a cascade of reactions – sympathetic activation, oxidative stress, systemic inflammation, endothelial dysfunction — which underlie cardiovascular complications (hypertension, atherosclerosis, arrhythmias), metabolic disturbances (insulin resistance, appetite-related hormonal imbalance), and neurocognitive consequences (daytime sleepiness, cognitive dysfunction).

KEYWORDS: *obstructive sleep apnea, pathophysiology, intermittent hypoxia, cardiovascular complications, metabolic disorders.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

ПАТОФИЗИОЛОГИЯ ОБСТРУКТИВНОГО АПНОЭ СНА

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РЕЗЮМЕ

Обструктивное апноэ сна (ОАС) — распространенное расстройство дыхания во сне, характеризующееся повторяющимися эпизодами обструкции верхних дыхательных путей, приводящими к апноэ и гипопноэ. В развитии ОАС участвует сочетание анатомических и функциональных факторов: сужение верхних дыхательных путей (например, из-за ожирения, краниофациальных особенностей), снижение тонуса мышц-глоточных дилататоров во сне, повышенная возбудимость дыхательного центра (нестабильность вентиляционного контроля, высокий loop gain) и низкий порог пробуждения. Эти факторы способствуют коллапсу глотки во сне с эпизодами гипоксии и пробуждениями. Повторяющаяся интермиттирующая гипоксия и фрагментация сна запускают каскад реакций – симпатическую активацию, оксидативный стресс, системное воспаление, эндотелиальную дисфункцию – что лежит в основе сердечно-сосудистых осложнений (гипертония, атеросклероз, аритмии), метаболических нарушений (инсулинорезистентность, дисбаланс гормонов аппетита) и нейрокогнитивных последствий (дневная сонливость, когнитивные нарушения).

КЛЮЧЕВЫЕ СЛОВА: обструктивное апноэ сна; патофизиология; интермиттирующая гипоксия; сердечно-сосудистые осложнения; метаболические нарушения.

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Introduction

Obstructive sleep apnea (OSA) is a syndrome in which recurrent partial or complete closure of the upper airway occurs during sleep, leading to cessation or reduction of pulmonary ventilation (apneas and hypopneas). These episodes cause a drop in blood oxygen saturation and activate stress responses, often culminating in brief awakenings (arousals). Epidemiological studies indicate that OSA is extremely common: globally, approximately 1 billion people aged 30–69 years are affected, with around 425 million having moderate to severe disease. The prevalence of OSA increases with age and is more frequent in men than in women (ratio approximately 2:1). The main risk factor is obesity: excessive fat deposition in the neck and pharyngeal region leads to airway narrowing, so the rise in body mass index correlates strongly with OSA risk. Other predisposing factors include neck circumference (>43 cm in men and >38 cm in women), craniofacial structural anomalies (micrognathia, retrognathia, narrow maxilla), tonsillar hypertrophy (especially important in childhood), chronic nasal obstruction, smoking, and meno-

pause in women. Family history and certain neurological disorders (neuropathies) may contribute to OSA by impairing the function of pharyngeal dilator muscles. Thus, OSA is a multifactorial condition arising at the intersection of anatomical predisposition and functional disturbances of respiratory regulation during sleep [1, 2].

The clinical manifestations of OSA — snoring, choking episodes during sleep, daytime sleepiness, fatigue, impaired concentration — are nonspecific; therefore, diagnosis requires instrumental verification (overnight polysomnography or respiratory monitoring. The importance of timely detection of OSA is dictated not only by its impact on quality of life but also by its long-term consequences. Repeated episodes of hypoxemia and arousals initiate a cascade of pathophysiological reactions leading to target-organ damage. OSA is considered an independent risk factor for a wide range of conditions — arterial hypertension, coronary artery disease, stroke, cardiac arrhythmias, heart failure, type 2 diabetes, nonalcoholic fatty liver disease, cognitive and behavioral disorders. Although epidemiological data convincingly demonstrate an increased risk of these disorders in OSA, whether treatment of OSA (e.g., CPAP therapy) reduces the incidence of cardiovascular events remains a matter of debate. This review presents current concepts of OSA pathogenesis and the systemic alterations caused by this condition, taking into account the strength of the available evidence. Particular attention is given to factors determining airway collapse during sleep and to the pathophysiological mechanisms underlying cardiovascular and metabolic complications in OSA [3].

Pathophysiological Mechanisms of OSA Development

Current concepts of OSA pathogenesis identify four major interrelated mechanisms: anatomical susceptibility to upper airway collapse, insufficient activity of pharyngeal dilator muscles, instability of ventilatory control, and abnormally low arousal threshold. Each of these factors contributes to sleep-related apnea in different patients to varying degrees.

Anatomical factors

Anatomical narrowing and increased compliance of the pharyngeal walls form the substrate for airway obstruction during sleep. While awake, pharyngeal muscle tone maintains airway patency; however, during sleep muscle tone falls, and in individuals with a narrow airway this leads to pharyngeal collapse — especially during inspiration due to negative intraluminal pressure. Patients with OSA frequently exhibit excessive fat deposition in the neck and pharyngeal regions associated with obesity, which mechanically narrows the airway and increases its collapsibility. In addition to obesity, anatomical contributors include craniofacial features — low hyoid position, retrognathia and micrognathia, narrow maxilla — as well as hypertrophy of the palatine tonsils and adenoids (particularly in children). These factors reduce the upper airway lumen and increase the likelihood of its closure during sleep.

Pharyngeal collapsibility is quantitatively described by the critical closing pressure (Pcrit): in healthy individuals, Pcrit is usually negative (< –5 cm H_2O), whereas in OSA it is often elevated to around 0 cm H_2O or even positive. In one study, average Pcrit in patients with severe OSA was – 0.3 cm H_2O compared with – 6.2 cm H_2O in healthy subjects. Notably, about 20% of patients with severe OSA had relatively non-collapsible airways (Pcrit – 2 to – 5 cm H_2O, i.e., near normal), and other pathophysiological abnormalities compensated for their limited anatomical impairment. Thus, anatomical predisposition is important but not the sole component of OSA pathogenesis [5, 6].

Neuromuscular factors

Maintenance of pharyngeal patency relies heavily on reflex activation of its dilator muscles. Normally, a decrease in airway pressure during inspiration elicits rapid reflex contraction of pharyngeal muscles (e.g., the genioglossus), counteracting collapse. In OSA, this compensatory response is often insufficient: dilator muscle activity during sleep fails to increase adequately in response to dropping pressure. Studies reveal that approximately 30–40% of OSA patients demonstrate markedly weakened or delayed genioglossus responses to negative pressure. One possible cause is neuropathy of pharyngeal mechanoreceptors from repeated traumatic collapses, reducing sensitivity and impairing the reflex arc. Additionally, chronic neuromuscular alterations (e.g., myopathy in obesity or age-related sarcopenia of pharyngeal muscles) may reduce airway functional performance. Consequently, some patients fail to generate sufficient increases in pharyngeal muscle tone during inspiration, promoting recurrent obstruction [7].

Ventilatory control instability

In some patients, OSA is significantly influenced by dysregulated central respiratory control — enhanced chemosensitivity leading to ventilatory instability. Normally, CO_2 accumulation after a hypopnea/apnea stimulates the respiratory center, restoring ventilation. However, when loop gain is high — reflecting an amplified ventilatory response — recovery becomes excessive: hyperventilation ensues, lowering CO_2 below baseline, which reduces respiratory drive and precipitates another apnea. This vicious cycle of hyperventilation–hypoventilation underlies periodic breathing. Elevated loop gain is observed in roughly one-third of OSA patients. In the aforementioned group of individuals with relatively non-collapsible airways, severe apnea was attributable to high loop gain: their respiratory center sensitivity to CO_2 was nearly twice that of patients with more pronounced anatomical defects. Ventilatory instability prolongs and increases the frequency of apneas, especially when combined with a low arousal threshold (see below). Therapeutically reducing loop gain (e.g., via oxygen therapy or acetazolamide) has lowered apnea severity in experimental settings, confirming this mechanism's relevance [7].

Low arousal threshold

Abnormalities in arousal processes also contribute to OSA pathogenesis. Some patients exhibit an excessively low arousal threshold: even minimal increases in breathing effort or slight hypoxia trigger awakening. On one hand, early arousal may limit apnea duration and the depth of desatura-

tion. On the other hand, frequent sleep interruptions exacerbate sleep fragmentation and sympathetic activation, sustaining a vicious cycle. Physiological studies indicate that roughly 30–40% of OSA patients have a pathologically low arousal threshold, contributing to chronic instability of sleep and breathing. The opposite scenario — an excessively high arousal threshold — occurs less commonly but may cause prolonged apneas with severe hypoxemia because the patient fails to awaken in time. Achieving an optimal balance of arousal reactivity is important for stabilizing sleep-related breathing. Pharmacological modulation of the arousal threshold (e.g., with non-benzodiazepine hypnotics to moderately increase it) has shown initial promise in reducing the apnea–hypopnea index in pilot studies [8].

Systemic Consequences and Complications of OSA

Recurrent hypoxic episodes and arousals in OSA initiate a complex array of pathological changes across multiple organs and systems. Below are the most significant consequences from a pathophysiological perspective and based on the available evidence.

Cardiovascular abnormalities

OSA is recognized as an independent risk factor for cardiovascular disease. Intermittent nocturnal hypoxia, fluctuations in intrathoracic pressure, and arousals activate the sympathetic nervous system and systemic inflammation, resulting over time in endothelial dysfunction, hypercoagulability, and atherogenesis. Chronic OSA is associated with the development of arterial hypertension, coronary artery disease, heart failure, stroke, and cardiac arrhythmias (particularly atrial fibrillation). In a major 10-year prospective study, untreated severe OSA significantly increased the risk of stroke and heart failure, independent of other risk factors. Meta-analyses of population studies also confirm that OSA is associated with a 20–30% increase in relative risk of fatal and nonfatal cardiovascular events. Chronic nocturnal hypoxemia is believed to play a central role by inducing inflammatory cytokine release, endothelial dysfunction, and accelerated atherosclerosis. Moreover, abrupt sympathetic surges during arousals lead to transient blood pressure spikes, fostering myocardial hypertrophy and vascular remodeling. Thus, OSA-related pathophysiological effects create strong preconditions for cardiovascular damage [9].

A substantial body of clinical data supports the association of OSA with cardiovascular disease. Observational studies show that patients with severe OSA exhibit increased prevalence and incidence of hypertension and other cardiac disorders compared with individuals without sleep apnea. Furthermore, treatment of OSA can improve certain surrogate markers: for example, CPAP typically reduces elevated blood pressure by 2–3 mmHg on average. However, results of large randomized controlled trials with hard endpoints have been less definitive. The SAVE trial (nearly 2700 patients) found no reduction in cardiovascular events (myocardial infarction, stroke) when CPAP was added to standard therapy in patients with cardiovascular disease and comorbid OSA. Limited adherence to CPAP and preexisting subclinical yet irreversible cardiovascular injury may have reduced intervention efficacy. Nonetheless, a meta-analysis using individual patient data demonstrated that patients with good CPAP adherence experience reduced risk of stroke and other complications compared with untreated individuals. Mandibular advancement devices and hypoglossal nerve stimulation used to treat OSA have also been linked to improvements in certain cardiovascular risk markers (e.g., heart rate variability, nocturnal blood pressure). Thus, while OSA is clearly associated with cardiovascular abnormalities, whether active treatment prevents major cardiovascular events remains an active area of research and expert discussion [8].

Metabolic effects

Obstructive sleep apnea is closely linked to obesity and components of the metabolic syndrome. More than 70% of OSA patients are overweight or obese, and apnea episodes themselves contribute to further weight gain through hormonal and metabolic shifts. Nocturnal hypoxia and sleep fragmentation activate stress pathways, promote insulin resistance, and impair glucose tolerance. Population-based studies show that moderate to severe OSA is associated with a 30–40% increased risk of developing type 2 diabetes over approximately 10 years of follow-up. This relationship persists even after adjusting for BMI, indicating an independent contribution of OSA to glucose dysregulation. Pathophysiologically, intermittent hypoxemia in OSA induces pro-oxidant and pro-inflammatory pathways (e.g., increasing expression of HIF-1α and NF-κB), driving systemic inflammation and dysfunction of white adipose tissue. As a result, insulin resistance develops, fasting insulin and glucose levels rise, and metabolic homeostasis is disrupted.

Chronic sleep loss and sympathetic activation also disturb leptin and ghrelin signaling — key appetite-related hormones — promoting overeating and further weight gain. Thus, a vicious cycle forms: OSA worsens metabolic disturbances, which in turn exacerbate apnea severity. Treatment can partially improve metabolic markers. In several studies, CPAP use reduced HbA1c levels in patients with diabetes, although findings across trials are inconsistent. Weight reduction remains the most effective intervention for breaking the OSA–metabolic syndrome connection. Intensive weight-loss programs or bariatric surgery have been shown to substantially reduce OSA severity (≥50% reduction in apnea–hypopnea index) while simultaneously improving insulin sensitivity and lipid profiles. This underscores the pivotal role of obesity as the shared pathophysiological mechanism linking OSA and metabolic disorders [10–12].

Neurocognitive and other consequences

OSA adversely affects central nervous system function. Chronic sleep fragmentation reduces slow-wave and REM sleep, manifesting as daytime sleepiness, impaired attention, memory deficits, and increased fatigue. Intermittent hypoxia damages neurons via oxidative stress and activation of programmed cell death. Patients with severe OSA demonstrate reduced gray matter volume in the hippocampus and prefrontal cortex, correlating with cognitive impairment. Clinically, this appears as deficits in executive function and increased

depressive and anxiety symptoms. OSA also significantly increases the risk of motor vehicle accidents due to daytime sleepiness — by 2–2.5 times according to meta-analyses. Treatment that improves sleep quality typically enhances cognitive performance and reduces daytime sleepiness, although some individuals retain residual deficits despite adequate CPAP therapy.

Another critical aspect is the relationship between OSA and stroke. In addition to raising stroke risk, OSA also worsens post-stroke recovery. Hypoxemic episodes aggravate ischemic brain injury and slow neuroplasticity. Therefore, screening and treatment for OSA are considered essential elements of stroke rehabilitation [13–15].

OSA also affects other organs and systems. Chronic intermittent hypoxia may impair kidney function, contributing to the progression of chronic kidney disease and refractory hypertension. Patients with severe OSA more frequently exhibit erectile dysfunction and decreased testosterone levels, attributed to hypoxemia and sleep fragmentation. A possible association between OSA and cancer risk has been proposed: some observational studies report higher cancer-related mortality in individuals with pronounced nocturnal hypoxemia. Intermittent hypoxia may stimulate angiogenesis and tumor progression, but current evidence remains inconsistent and insufficient for definitive conclusions. Additionally, OSA worsens the course of chronic diseases — e.g., type 2 diabetes, chronic obstructive pulmonary disease (the "overlap syndrome"), and obesity hypoventilation syndrome (Pickwick syndrome). The coexistence of OSA and COPD leads to higher rates of pulmonary hypertension and respiratory failure, making recognition and treatment of OSA crucial in such patients [14].

Prospects for Personalized Therapy

Modern understanding of OSA pathophysiology creates opportunities for personalized treatment approaches. CPAP remains the standard therapy, effectively reducing apnea severity in most patients. However, tolerance to CPAP is often limited, and some patients have residual symptoms despite treatment. Since OSA is a heterogeneous disorder, identifying the predominant pathophysiological mechanism in each individual enables targeted alternative interventions. Distinguishing phenotypic "endotypes" of OSA (predominantly anatomical, neuromuscular, ventilatory control instability, or low arousal threshold) is important for therapy selection.

For patients in whom anatomical abnormalities predominate (e.g., craniofacial anomalies or tonsillar hypertrophy), surgical interventions can significantly improve outcomes. In adults, uvulopalatopharyngoplasty and its modern variants, as well as airway-expansion surgeries (e.g., mandibular expansion), are widely used. In children, adenotonsillectomy is often the first-line treatment, relieving nasopharyngeal obstruction. For positional OSA, positional therapy devices that prevent supine sleep are effective [16].

When low pharyngeal muscle activity is the primary issue, hypoglossal nerve stimulation emerges as a promising therapy. Implantable stimulators periodically activate the genioglossus during sleep to prevent airway collapse. Clinical trials (e.g., the STAR trial) demonstrated >50% reduction in apnea–hypopnea index in patients intolerant to CPAP. Myofunctional therapy — specialized exercises for the tongue and pharyngeal muscles — can also improve muscle tone and moderately reduce OSA severity [17].

For patients with high loop gain (ventilatory control instability), approaches targeting respiratory center sensitivity are being studied. Supplemental nocturnal oxygen can reduce ventilatory oscillations and decrease apnea frequency in such patients. Respiratory stimulants (e.g., acetazolamide), effective in high-altitude periodic breathing, are currently under investigation for OSA.

Finally, in patients with excessively low arousal thresholds, cautious pharmacological elevation of this threshold is of interest. Low doses of certain hypnotics (zopiclone, eszopiclone) have increased sleep stability without worsening breathing in clinical studies, allowing apnea to persist long enough for airway patency to be restored without arousal, thereby improving ventilation. In a pilot randomized trial, adding eszopiclone to CPAP in patients with low arousal threshold yielded an additional 30% reduction in apnea–hypopnea index compared with CPAP alone [18].

The approaches described above reflect a shift toward personalized OSA therapy based on pathophysiological profiling. Combinations of methods (e.g., mild sedative + oxygen to raise arousal threshold and reduce loop gain) have shown synergistic effects in small studies. Development of precision-medicine algorithms is expected to enhance treatment efficacy and overcome limitations of CPAP. Simplified diagnostic tests for OSA phenotyping (such as determining critical pressure via CPAP dial-down or testing oxygen sensitivity) are already being proposed for clinical practice. These tools may allow clinicians to prescribe targeted alternative or adjunctive therapies based on the dominant mechanism of obstruction [19, 20].

Conclusion

Obstructive sleep apnea is a complex, multifactorial condition affecting multiple levels of respiratory regulation — from upper airway anatomy to neuroreflex mechanisms. Understanding of OSA pathophysiology has advanced considerably in recent years, enabling identification of phenotypic variants and the development of personalized treatment strategies. OSA is associated with increased risk of cardiovascular, metabolic, and neurocognitive complications, although the extent of these effects and their reversibility vary according to patient characteristics and comorbidities. Modern management of OSA requires a multidisciplinary approach integrating lifestyle modification, device-based and surgical interventions, and when necessary, pharmacological agents targeting specific pathophysiological pathways. Large prospective studies remain essential to clarify long-term effects of OSA treatment on the prevention of myocardial infarction, stroke, and other outcomes, as well as to optimize therapeutic combinations. Nevertheless, existing evidence underscores that recognition and treatment of OSA are crucial for improving long-term prognosis and quality of life. Ongoing research in OSA pathophysiology promises further refinement of treatment strategies and improved patient outcomes.

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