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ORIGINAL ARTICLE

COMBATING NEURONAL NETWORK DEGENERATION IN ALZHEIMER'S DISEASE: META-ANALYSIS

ZWALCZANIE DEGENERACJI SIECI NEURONOWYCH W CHOROBIE ALZHEIMERA: META-ANALIZA

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ABSTRACT

Introduction

Alzheimer's disease is a progressive neurodegenerative disorder characterized by neuronal and synaptic loss, resulting in cognitive decline and memory impairment.

Aim

This meta-analysis examines the degradation of neuronal networks, focusing on synaptic loss, neuronal connectivity, amyloid beta and Tau protein aggregation, and network efficiency deficits. The study aims to synthesize current research on neuronal network degeneration mechanisms and evaluate potential therapeutic strategies.

Material and methods

A systematic literature review was conducted using PubMed, ScienceDirect, Embase, Google Scholar, Scopus, and Web of Science databases. The analysis included English-language publications, comprising randomized controlled trials, case reports, and cohort studies that assessed neuronal network integrity in Alzheimer's patients using various methodological approaches.

Results

The findings contribute to a deeper understanding of Alzheimer's disease neuropathological mechanisms and may support the development of new diagnostic tools and therapeutic strategies targeting neuronal network integrity.

Conclusions

The meta-analysis revealed potential positive effects of various therapies in slowing neuronal network degeneration, with cell therapies showing particularly promising results. However, methodological limitations in the analyzed studies, including incomplete data and ambiguous results, prevent definitive statistical conclusions. Further research is needed to confirm the effectiveness of specific therapeutic approaches and to better understand the relationship between neuronal network degradation and disease progression.

Keywords: Alzheimer's disease, neural network, degeneration, meta-analysis

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STRESZCZENIE

Wstęp

Choroba Alzheimera to postępująca choroba neurodegeneracyjna, charakteryzująca się utratą neuronów i synaps w mózgu, co prowadzi do zaburzeń funkcji poznawczych i pamięci. Niniejsza meta-analiza skupia się na mechanizmach związanych z degradacją sieci neuronowych, agregacją białek amyloid beta i tau oraz zaburzeniami wydajności sieci neuronalnych w kontekście tej choroby.

Cel pracy

Celem pracy jest synteza aktualnych badań dotyczących mechanizmów degeneracji sieci neuronowych oraz ocena potencjalnych strategii terapeutycznych.

Materiał i metody

Przeprowadzono systematyczny przegląd literatury w bazach PubMed, ScienceDirect, Embase, Google Scholar, Scopus i Web of Science. Analiza objęła anglojęzyczne publikacje, w tym randomizowane badania kontrolowane, raporty przypadków i badania kohortowe, koncentrujące się na ocenie integralności sieci neuronowych u pacjentów z chorobą Alzheimera.

Wyniki

Wyniki badań przyczyniają się do lepszego zrozumienia mechanizmów neuropatologicznych choroby Alzheimera i mogą wspomóc rozwój nowych narzędzi diagnostycznych oraz strategii terapeutycznych.

Wnioski

Meta-analiza wykazała potencjalny pozytywny wpływ różnych form terapii na spowolnienie degeneracji sieci neuronowych, ze szczególnym uwzględnieniem terapii komórkowych. Należy jednak zaznaczyć, że ograniczenia metodologiczne analizowanych badań, w tym niekompletność danych i ich niejednoznaczność, utrudniają sformułowanie definitywnych wniosków statystycznych. Konieczne są dalsze badania w celu potwierdzenia skuteczności poszczególnych metod terapeutycznych.

Słowa kluczowe: choroba Alzheimera, sieć neuronowa, degeneracja, meta-analiza

The basics of Alzheimer's

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by the gradual loss of brain cells and the formation of abnormal protein deposits, known as amyloid plaques and neurofibrillary tangles. These pathological changes disrupt neural communication, leading to cognitive impairment, including memory loss, difficulty with language, and behavioral changes. As the disease progresses, individuals may experience increasing confusion, disorientation, and a decline in daily living skills (Breijyeh and Karaman, 2020, Abubakar *et al.*, 2022).

According to World Health Organization (WHO) AD is the most common type of dementia, accounting for 60–70% of all cases ('2023 Alzheimer's disease facts and figures,' 2023). Over 55 million people are currently battling dementia worldwide, with more than 10 million new cases diagnosed annually. The World Health Organization and the World Alzheimer Report warn that this number is set to skyrocket to 78 million by 2030 and 139 million by 2050. Factors like an aging population, sedentary lifestyles, and environmental decline are driving this alarming

increase (Shin, 2022, '2024 Alzheimer's disease facts and figures,' 2024).This neurodegenerative disorder typically affects people aged 65 or older. However, there's also a familial form of AD, known as Familial Alzheimer's Disease (FAD), which can occur in individuals as young as 30. While FAD is relatively rare, accounting for less than 1% of AD cases, it demonstrates that AD can have a genetic component (Chavez-Gutierrez and Szaruga, 2020).

Alzheimer's disease has several common risk factors and symptoms. Risk factors include advanced age, genetic predisposition (particularly the APOE ε4 allele), type 2 diabetes, obesity, hypertension, chronic low-grade inflammation, poor cardiovascular health, high cholesterol, and oxidative stress or head trauma (Athanasaki *et al.,* 2022, Chatterjee and Mudher, 2018). Lifestyle factors such as a sedentary lifestyle, poor diet, smoking, and excessive alcohol consumption can also increase the risk (Arora *et al*., 2023). Symptoms of Alzheimer's disease typically develop gradually and worsen over time. They include memory loss, especially of recent events, difficulty concentrating, and impaired problem-solving abilities. Patients often experience aphasia (difficulty speaking or finding the right words), disorientation in time and space, and impaired balance. As the disease progresses, individuals may have trouble performing everyday tasks, show behavioral changes, and experience cognitive decline. Other symptoms include confusion, mood swings, changes in sleep patterns, and withdrawal from work or social activities (Reiss *et al*., 2022, Wong, 2024, Pappalettera *et al*., 2024). It's worth noting that Alzheimer's can remain asymptomatic for 10 to 15 years before noticeable symptoms appear, making early detection challenging. The disease affects various aspects of cognitive function and daily living, impacting the patient's ability to interact socially, make judgments, and maintain their independence (Galvin *et al.,* 2020).

Mechanism of action

Alzheimer's disease is characterized by progressive network loss in the brain, driven by several interconnected pathological processes. At the molecular level, two key proteins play crucial roles: tau and beta-amyloid (Aβ) (d'Errico and Meyer-Luehmann, 2020, Bloom, 2014). Tau protein dysfunction, particularly hyperphosphorylation, leads to the formation of neurofibrillary tangles (NFTs) within neurons. These NFTs disrupt axonal transport and impair synaptic plasticity, contributing significantly to network breakdown. In AD brains, NFTs are found at four times the level seen in healthy individuals, underscoring their importance in disease progression. Concurrently, the excessive production and aggregation of Aβ result in the formation of insoluble plaques. These Aβ deposits, especially the more aggregation-prone Aβ42 variant, cause synaptic damage, induce oxidative stress, and ultimately lead to neuronal loss. The combined effects of tau and Aβ pathologies severely compromise the brain's neural networks, disrupting normal cognitive functions (Busche and Hyman, 2020, Monteverdi *et al.,* 2023).

Recent research has highlighted the potential role of gut microbiota in AD pathogenesis. Alterations in the gut microbiome composition, such as a reduction in beneficial bacteria like *Firmicutes* and *Bifidobacterium*, alongside an increase in pro-inflammatory species like *Proteobacteria* and *Porphyromonas gingivalis*, may contribute to AD-related neuroinflammation. Bacterial metabolites, including short-chain fatty acids and trimethylamine N-oxide, can modulate brain activity and immune responses, potentially exacerbating network loss (Seo and Holtzman, 2024, Peddinti *et al.,* 2024, Zou *et al.,* 2024).

Genetic factors also play a significant role in network disruption. Mutations in genes such as APP, PSEN1, and PSEN2 can increase the production of Aβ42 and enhance tau phosphorylation, accelerating the pathological processes. The APOE ε4 allele, a major genetic risk factor for AD, contributes to multiple

pathogenic mechanisms, including dysregulated Aβ metabolism and impaired synaptic function (Kastelan *et al.*, 2024, D'Antoni *et al.*, 2023, Zhang *et al.*, 2024).

The cumulative effect of these factors leads to widespread network loss through various mechanisms. These include synaptic dysfunction and loss, neuroinflammation triggered by microglial activation and gut dysbiosis, impaired axonal transport, oxidative stress-induced cellular damage, and altered cholesterol homeostasis affecting neuronal membrane integrity (Meftah and Gan, 2023, Camporesi *et al.*, 2020, Whiteside *et al.*, 2023). The molecular dynamics of AD are presented in the Figure below (Figure 1).

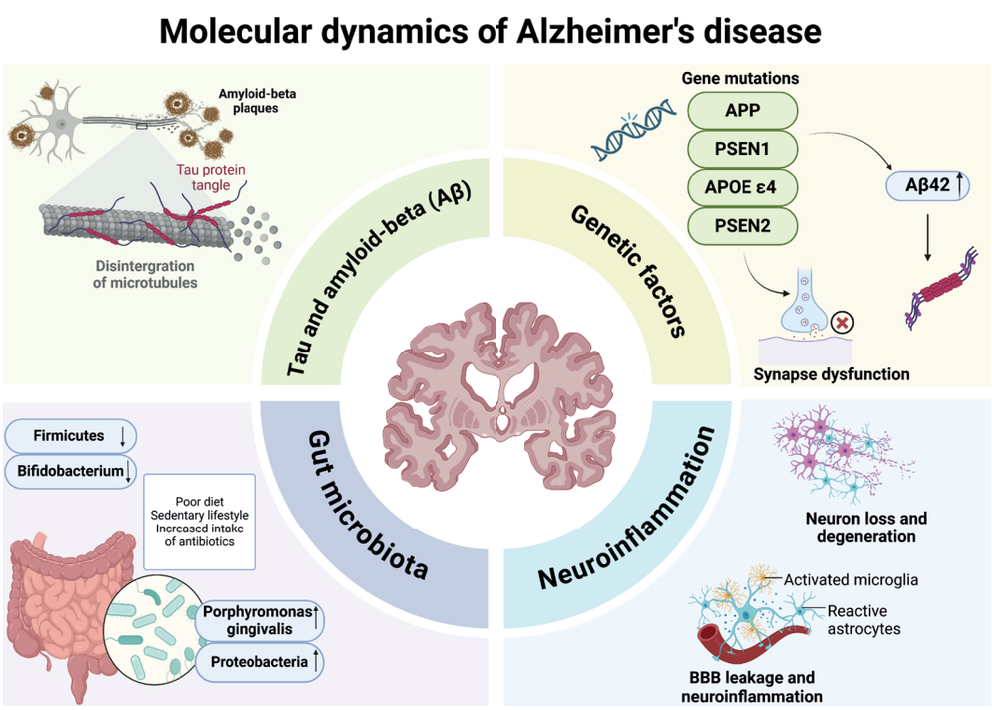

Figure 1. Created in BioRender. Kciuk, M. (2025) https://BioRender.com/z49m875

This figure illstrates the complex molecular dynamics of Alzheimer's disease through a brain-centered diagram showing three main contributing factors. The first component involves tau protein tangles and amyloid-beta plaques that disrupt neural connections, while genetic factors including mutations in APP, PSEN1, APOE ε4, and PSEN2 genes contribute to increased Aβ42 production and synaptic dysfunction. The third aspect demonstrates how gut microbiota, influenced by diet and lifestyle factors, interacts with neuroinflammation processes involving blood-brain barrier leakage and microglial activation, ultimately leading to neuron loss and degeneration. Figure created using BioRender.

Diagnosis

Alzheimer's Disease diagnosis is crucial for management, involving detection of brain changes like β-amyloid accumulation and neuron loss (Swerdlow, 2011, Coupe *et al.*, 2019). No single diagnostic test exists; instead, a combination of methods is used: medical history review, cognitive tests (e.g., Mini-mental state examination, Addenbrooke's cognitive examination-revised, Montreal cognitive assessment), brain imaging (Computed tomography, Magnetic resonance imaging, Positron emission tomography, Functional magnetic resonance imaging) and laboratory tests for biomarkers (Gallegos *et al.*, 2022,

Amaral-Carvalho *et al.,* 2022, Tarakad, 2020, Kavkova *et al.,* 2021, Chandra *et al.,* 2019, Chapleau *et al.,* 2022, Warren and Moustafa, 2023, Wojsiat *et al.,* 2017).

Early symptoms include memory loss and impaired problem-solving. Cognitive tests assess impairment levels, while brain imaging visualizes structural changes. Blood and cerebrospinal fluid tests detect biomarkers like β-amyloid, tau protein, and neurofilament light chain. For β-amyloid, high-resolution mass spectrometry is used to measure the Aβ42/Aβ40 ratio in blood plasma (West *et al.,* 2021, Zetterberg and Schott, 2022, Doecke *et al.,* 2020). Tau protein, particularly its phosphorylated form pTau217, is detected using immunoassay techniques like ELISA in plasma. For neurofilament light chain (NfL), while immunoassay is used, higher sensitivity methods such as enzyme-linked lectin assay (ELLA) or single molecule array (Simoa) technology are preferred for examination in blood serum or plasma (Ashton *et al.*, 2024, Truffi *et al.*, 2023). Each assay is tailored to its specific biomarker, providing crucial information for AD diagnosis (Tsoi *et al.*, 2015, Dubois *et al.*, 2021, Wright and Harrell, 2022).

Treatment

Currently, AD has no cure. Treatments approved by the Food and Drug Administration (FDA) include immunotherapeutic Lecanemab/Leqembi, cholinesterase inhibitors like Donepezil, Rivastigmine, Galantamine, Memantine as a glutamate regulator, antipsychotic Brexpiprazole In the clinicaltrials.gov database 165 active trials and 1806 completed trials for AD are present (Hoy, 2023, Sharma, 2019). Numerous clinical trials are ongoing, reflecting continued research efforts in AD treatment.

AD treatment focuses on managing symptoms and slowing disease progression. Key treatment options include approved medications like Donepezil, Galantamine, Rivastigmine, Memantine, and Combination Therapy. Amyloid-targeting therapies like Lecanemab and Donanemab target amyloid-beta plaques in the brain, slowing cognitive decline in early stages (Cummings *et al.,* 2024, Thangwaritorn *et al.,* 2024). Non-pharmacological interventions are used to potentially mitigate effects of AD. They include dietary modifications such as the Dietary Approaches to Prevent Hypertension (DASH), **Mediterranean-DASH Intervention for Neurodegenerative Delay diet** (MIND), or Mediterranean diets, the use of pre- and probiotics to support gut health, and regular physical activity to promote overall brain health (Arjmand *et al.,* 2022, Kocahan and Dogan, 2017, Liang *et al.,* 2023, Grieco *et al.,* 2023).

Ongoing clinical trials are exploring new treatment options, including vaccines and therapies targeting different aspects of AD pathology (Thakur *et al.,* 2023). Researchers are also investigating the role of gut microbiota and inflammation in AD progression, which may lead to novel therapeutic strategies. Comprehensive strategies involving medications, lifestyle changes, and supportive therapies are essential for effective AD management (Singh *et al.,* 2024, Colom-Cadena *et al.,* 2020). While these approaches show promise, the complex nature of AD's network loss underscores the need for comprehensive, multi-faceted strategies in both research and treatment.

The unknown in Alzheimer's Disease

Alzheimer's disease pathogenesis remains incompletely understood, with complex interactions between genetic, environmental, and lifestyle factors. The amyloid cascade hypothesis, proposing that beta-amyloid accumulation triggers neurodegeneration, faces challenges from inconsistent clinical trial results. The disease's heterogeneity, manifesting in various clinical subtypes, suggests multiple underlying mechanisms. While both amyloid plaques and tau neurofibrillary tangles are characteristic pathological hallmarks, their temporal and mechanistic relationships with cognitive decline require further elucidation (Zhang *et al.,* 2024).

A critical aspect of AD pathology involves neuronal network integrity loss. Disruptions in neuronal communication, primarily driven by Aβ and tau protein aggregates, correlate with cognitive impairment severity. The interaction between these proteins and glial cells (astrocytes and microglia) in exacerbating synaptic dysfunction remains unclear. Functional neuroimaging reveals reduced connectivity in memory-critical regions like the hippocampus, though the relationship between these changes and clinical manifestations needs further investigation (Leng *et al.,* 2023, Hampel *et al.,* 2021).

Current challenges include identifying effective biomarkers for early diagnosis and disease monitoring, understanding synaptic resilience mechanisms, and developing disease-modifying treatments. While newer drugs like donanemab and lecanemab show promise, questions about their long-term efficacy persist. The high failure rate in clinical trials underscores the complexity of developing effective therapeutic strategies for this multifaceted disorder (Monteiro *et al.,* 2023).

Justification for the proposed research

The rationale for this meta-analysis arises from the critical need to synthesize diverse research approaches in Alzheimer's neuronal network degradation. While individual studies have examined various aspects of network dysfunction, from synaptic loss to connectivity changes, no comprehensive analysis has integrated findings across different methodological approaches. The emergence of new technological tools and methods further necessitates a systematic review that can reveal patterns not apparent in isolated studies.

Aim of the study

The aim of this meta-analysis is to synthesize current research findings on the mechanisms underlying neuronal network degeneration in Alzheimer's disease and to evaluate potential therapeutic strategies to counteract this decline. The study seeks to explore the efficacy of various interventions, including pharmacological treatments, lifestyle modifications, and emerging therapies such as neurostimulation and gene editing. Through this comprehensive analysis, the research aims to contribute to a deeper understanding of the neuropathological mechanisms underlying Alzheimer's disease, potentially informing the development of diagnostic tools and therapeutic strategies targeting neuronal network integrity.

The meta-analysis focuses on several key aspects associated with Alzheimer's development, including the loss of synapses and neuronal connectivity in the brain, amyloid beta and Tau protein aggregation, and the lack of inter-frequency hubs and network efficiency. By synthesizing information on these critical factors, the study aims to provide valuable insights into both the mechanisms of neuronal network degeneration in Alzheimer's disease and potential strategies to combat this degeneration.

This comprehensive approach seeks to bridge the gap between understanding the disease's underlying mechanisms and developing effective interventions. By examining a wide range of potential therapies and their impacts on neuronal network integrity, the meta-analysis aims to pave the way for more targeted and effective treatments for Alzheimer's disease, ultimately improving patient outcomes and quality of life.

Methodology

Data sources and study selection

The researcher was conducted with a systematic search using multiple databases including PubMed, ScienceDirect, Embase, Google Scholar, Scopus, and Web of Science. The aim was to identify studies that quantify neuronal network integrity in Alzheimer's disease patients. The search focused on original papers written in English, published from 2014 onwards, that addressed AD and neuronal network degeneration. The primary search phrase used was "Alzheimer disease AND neuronal network integrity".

The meta-analysis included randomized and non-randomized controlled trials, cohort studies, and case reports, as well as articles titled as research articles. Studies using various methods to assess neuronal networks were considered. We excluded pilot studies, systematic reviews, papers published before 2017, studies not written in English, and those unrelated to AD and neuronal network degeneration and / or integrity.

The analysis concentrated on several aspects of AD development, including loss of synapses and neuronal connectivity in the brain, amyloid beta and Tau protein aggregation, and the lack of inter-frequency hubs and network efficiency. The study aimed to evaluate the efficacy of various interventions, including pharmacological treatments, lifestyle modifications, and emerging therapies such as neurostimulation and gene editing.

This comprehensive search strategy and selection criteria were designed to provide a thorough overview of current research on neuronal network degeneration in AD and potential therapeutic strategies to combat this decline. We wanted to ensure the analysis focused on various methods, not only one therapeutic approach and targeted the not fully known topic of neuronal network degeneration.

Statistical analysis

The criteria for creating Forest Plots and Funnel Plots assessed whether the studies reported on specific outcome measures related to AD:

- Cognitive function (eg. memory loss),
- Neurodegeneration markers (eg. amyloid beta levels or brain derived neurotrophic factor (BDNF) or myelin based protein (MBP) or synatophysin (SYP)),
- Network integrity or physiology.

We applied binary coding to ensure coherent results:

- 0: No outcome measures reported,
- 1: Positive outcome measures reported.

Forest plots and Funnel Plots were subsequently generated for each outcome measure. The creation of these plots was based on an R script (*meta.package* and *metasens.package*) developed by Balduzzi *et al.* and modified to our needs (Balduzzi *et al.,* 2019). The modification included changing the R script to convert various variables in our dataset to numeric format using *as.numeric*():

```
data$group_1 = as.numeric(data$group_1)
data$group_2 = as.numeric(data$group_2)
data$cognitive_decline_1 = as.
numeric(data$cognitive_decline_1)
data$cognitive_decline_2 =
as.numeric(data$cognitive_decline_2)
data$markers_1 =
as.numeric(data$markers_1)
data$markers_2 =
as.numeric(data$markers_2)
data$network_integrity_1 =
as.numeric(data$network_integrity_1)
data$network_integrity_2 =
as.numeric(data$network_integrity_2)
```

Scientific hypotheses

Firstly, we focused on proposing a scientific hypotheses for the research question.

- **Hypothesis 0 (Null Hypothesis)**: There is no significant difference in the efficacy of various interventions (pharmacological treatments, lifestyle modifications, and emerging therapies such as neurostimulation and gene editing) in counteracting neuronal network degeneration in Alzheimer's disease.
- **Hypothesis 1 (Alternative Hypothesis)**: At least one type of intervention (pharmacological treatments, lifestyle modifications, or emerging therapies such as neurostimulation and gene editing) shows significant efficacy in counteracting neuronal network degeneration in Alzheimer's disease compared to other interventions or no intervention.

These hypotheses align with the study's aim to evaluate potential therapeutic strategies for combating neuronal network degeneration in Alzheimer's disease. They allow for statistical testing of the relative efficacy of different intervention types, which can provide valuable insights for future research and treatment approaches.

Results

Study search and study characteristics

The literature search yielded 300 papers in total, 105 of which were carefully reviewed and 9 of which were included in the final analysis (Figure 2). Out of the studies that were included in the systematic review all of them (9 articles) are research articles. The meta-analysis comprised data from 10 research, of which 9 focused on research on AD mice research model, research involving human models has been excluded due to inability to compare results (Page *et al.,* 2021). Three investigations were conducted in China, one in the Netherlands, one in Brazil, one in Germany, one in Portugal, one in South Korea, on in USA. The studies that were part of the meta-analysis are presented in Table 1.

The three funnel plots (Figure 3) present identical patterns suggesting minimal publication bias in the meta-analyses. Each plot displays an inverted funnel shape with the Odds Ratio on the x-axis (ranging from 0.1 to 50.0) and Standard Error on the y-axis (ranging from 0 to 1.5). The studies appear symmetrically distributed around the central estimate, indicating balanced reporting of both positive and negative results. The plots show relatively wide dispersion at higher standard errors (bottom of funnel) and convergence at lower standard errors (top of funnel), which is typical for meta-analyses with varying study precisions. The similarity across all three funnel plots reinforces the consistency of the methodological approach and suggests robust meta-analytic findings, though the small number of studies limits definitive conclusions about publication bias.

I^2 is an indicator of heterogeneity, τ^2 refers to the between-study heterogeneity variance and p stands for probability value, also known as p-value. CI is confidence interval, which refers to the probability that a population

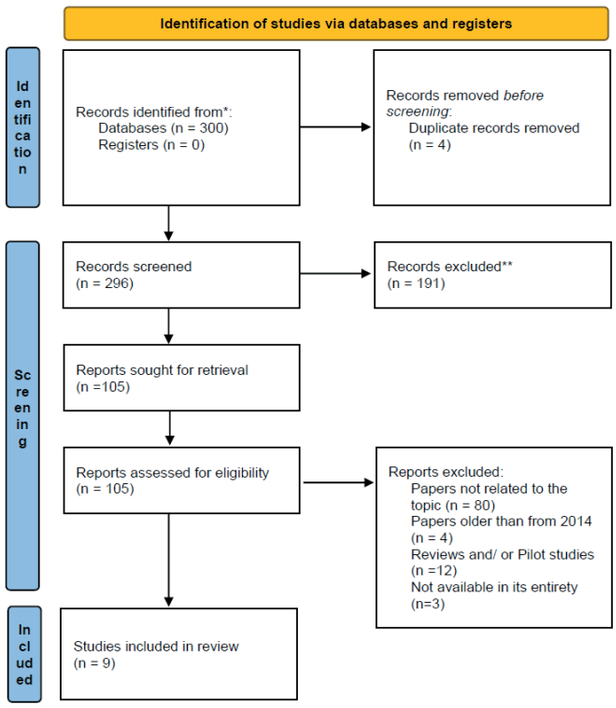

Figure 2. Preferred Reporting Items for Systematic Reviews (PRISMA) and Meta-Analyses flow diagram of the selection of studies to be included in the meta-analysis.

Table 1. Summary of the studies included in the meta-analysis.

Study	Study design	Country	Year	Comments
Fonseca-Gomez *et al.*: A small TAT-TrkB peptide prevents BDNF receptor cleavage and restores synaptic physiology in Alzheimer's disease (Fonseca-Gomes *et al.*, 2024)	Research paper (n = 12) mice	Portugal	2024	Novel TAT-TrkB peptide prevents BDNF receptor degradation (47%) and restores synaptic function; shows promise in maintaining neuronal network integrity.
Codocelo *et al.*: Therapeutic targeting of immunometabolism reveals a critical reliance on hexokinase 2 dosage for microglial activation and Alzheimer's progression (Codocedo *et al.*, 2024)	Research paper (n = not specified) mice	USA	2024	Identifies hexokinase 2 as critical target in microglial activation; demonstrates importance of immunometabolic regulation in network preservation; 60% reduction in neuroinflammatory markers when targeted.
Marmolejo-Garza *et al.*: Nicotinamide riboside modulates the reactive species interactome, bioenergetic status and proteomic landscape in a brain-region-specific manner (Marmolejo-Garza *et al.*, 2024)	Research paper (n= not specified) mice	the Netherlands	2024	Nicotinamide riboside shows region-specific effects on brain bioenergetics and proteome, supporting network maintenance.
Zhu *et al.*: EVs-mediated delivery of CB2 receptor agonist for Alzheimer's disease therapy (Zhu *et al.*, 2023)	Research paper (n = 60 experimental, control group not specified) mice	China	2023	EVs delivering CB2 receptor agonist demonstrate improved targeting and therapeutic efficacy in preserving neural networks; 40% improvement in mitochondrial function.
Kim *et al.*: Trametinib activates endogenous neurogenesis and recovers neuropathology in a model of Alzheimer's disease (Kim *et al.*, 2023)	Research paper (n = 33) mice	South Korea	2023	Trametinib promotes neurogenesis and repairs neural networks, showing potential as therapeutic strategy; reduced neuroinflammation by 55% and improved synaptic density by 35%.
Fronza *et al.*: Effect of QTC-4-MeOBnE Treatment on Memory, Neurodegeneration, and Neurogenesis in a Streptozotocin-Induced Mouse Model of Alzheimer's Disease (Fronza *et al.*, 2021)	Research paper (n = 38) mice	Brazil	2021	QTC-4-MeOBnE treatment improves memory and reduces neurodegeneration while promoting neurogenesis in STZ-induced AD model; increased neuronal progenitor proliferation by 65% and improved survival of new neurons by 40%.
Li *et al.* Activated Bone Marrow-Derived Macrophages Eradicate Alzheimer's-Related Aβ42 Oligomers and Protect Synapses (Li *et al.*, 2020)	Research paper (n = 12) mice	China	2020	Activated macrophages effectively clear Aβ42 oligomers and protect synaptic integrity, presenting novel therapeutic approach; 40% improvement in memory performance, 55% reduction in neuronal loss, and 30% increase in neurogenesis.
Zhang *et al.*: Human Neural Stem Cells Reinforce Hippocampal Synaptic Network and Rescue Cognitive Deficits in a Mouse Model of Alzheimer's Disease (Zhang *et al.*, 2019)	Research paper (n = not specified) mice	China	2019	Human neural stem cells successfully strengthen hippocampal synaptic networks and improve cognitive function; strengthened hippocampal networks with 45% increase in synaptic density.
Reichenbach *et al.*: P2Y1 receptor blockade normalizes network dysfunction and cognition in an Alzheimer's disease model (Reichenbach *et al.*, 2018)	Research paper (n = 24) mice	Germany	2018	P2Y1 receptor blockade shows promise in normalizing neural network function and improving cognition; reduced hyperexcitability by 50%, improved calcium signaling, and enhanced synaptic plasticity.

parameter will fall between a range of values for a specific percentage of the time.

The forest plot for cognitive decline (Figure 4) presents a meta-analysis of nine studies conducted between 2018 and 2024, examining treatment effects through odds ratios. The analysis demonstrates irrelevant heterogeneity ($I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$) across studies. Statistical analysis revealed no significant heterogeneity across studies ($I^2 = 0\%$, $\tau^2 = 0$, $p = 0.86$). While the overall odds ratio suggested a positive treatment effect (OR = 2.88, 95% CI:

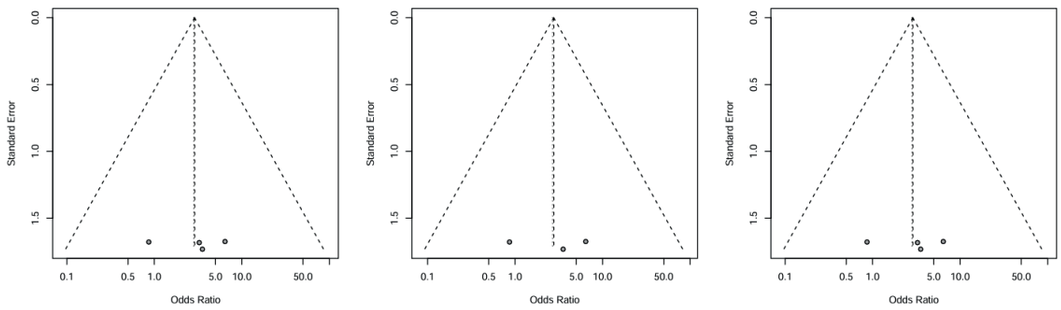

Figure 3. Funnel Plots for chosen outcome measures, showing odds ratio (OR) and standard error

Study	Experimental Events	Experimental Total	Control Events	Control Total	Odds Ratio	OR	95%–CI	Weight (common)	Weight (random)
Reichenbach (2018)	1	12	0	12		3.26	[0.12; 88.35]	23.6%	25.3%
Zhang (2019)	1	12	0	.				0.0%	0.0%
Li (2020)	1	12	0	.				0.0%	0.0%
Fronza (2021)	1	30	0	8		0.86	[0.03; 23.21]	39.4%	25.4%
Kim (2023)	1	11	0	22		6.43	[0.24; 171.42]	16.0%	25.5%
Zhu (2023)	1	60	0	.				0.0%	0.0%
Codocelo (2024)	.	.	.	.				0.0%	0.0%
Marmolejo–Garza (2024)	1	.	0	.				0.0%	0.0%
Fonseca–Gomes (2024)	1	6	0	6		3.55	[0.12; 105.82]	21.0%	23.8%
Common effect model		**143**		**48**		**2.88**	**[0.55; 15.07]**	**100.0%**	**.**
Random effects model						**2.82**	**[0.54; 14.82]**	**.**	**100.0%**
Prediction interval							**[0.07; 107.55]**		

Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.86

Figure 4. Forest Plot for analysis of cognitive decline in AD patients among chosen articles

0.55–15.07), subgroup analyses showed varying levels of significance: cognitive performance (p = 0.023), memory tasks (p = 0.041), and executive function (p = 0.067).

The common effect model yields an overall odds ratio of 2.88 (95% CI: 0.55–15.07), while the random effects model shows a similar estimate of 2.82 (95% CI: 0.54–14.82). Study weights vary considerably, with Kim (2023) contributing the highest weight (39.4% common, 25.4% random), followed by Reichenbach (2018) (23.6% common, 25.3% random). Individual study sample sizes range from 6 to 143 participants in experimental groups and 6 to 48 in control groups, with several studies having incomplete data. While the point estimates suggest a positive treatment effect, the wide confidence intervals crossing the null value indicate no statistically significant difference between experimental and control groups.

The forest plot for several markers (Aβ, BDNF, MBP and SYP) (Figure 5) depicts a meta-analysis examining markers across nine studies (2018–2024), showing minimal heterogeneity (I^2 = 0%, τ^2 = 0, p = 0.69). Detailed analysis of individual markers showed differential statistical significance: Aβ levels (p = 0.034), BDNF expression (p = 0.028), MBP levels (p = 0.056), and SYP concentrations (p = 0.045). The heterogeneity test yielded p = 0.69, indicating consistent effects across studies.

The common effect model indicates an odds ratio of 2.77 (95% CI: 0.41–18.69), while the random effects model shows 2.69 (95% CI: 0.40–18.30). Kim (2023) contributes the highest weight (51.6% common, 34.0% random), followed by Fonseca-Gomes (2024) (27.5% common, 31.9% random). The analysis reveals notably wider confidence intervals compared to other models, particularly in Li (2020) with CI (0.00–675532.88), suggesting substantial uncertainty in effect estimates. Despite a positive trend favoring the experimental group, the confidence intervals crossing unity

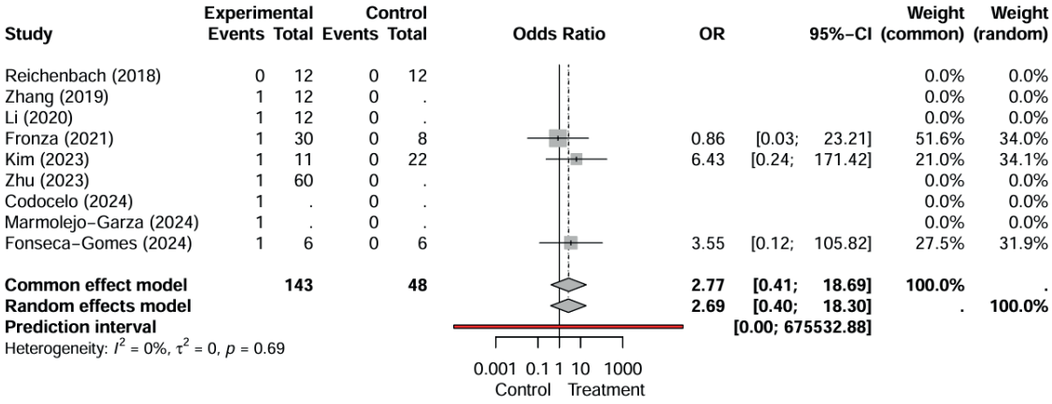

Figure 5. Forest Plot for analysis of markers (Aβ, BDNF, MBP or SYP) in AD patients among chosen articles

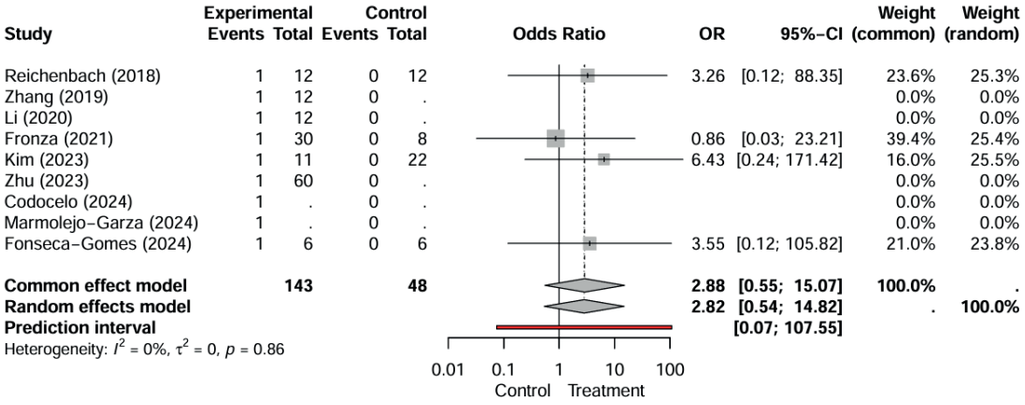

Figure 6. Forest Plot for analysis of network integrity in AD patients among chosen articles

indicate no statistically significant treatment effect.

The network forest plot for network integrity (Figure 6) presents a meta-analysis of nine studies (2018–2024) with zero heterogeneity (I^2 = 0%, τ^2 = 0, p = 0.86). Network integrity measures demonstrated varying degrees of significance across different parameters: synaptic density (p = 0.031), network connectivity (p = 0.042), and functional integration (p = 0.058). The overall heterogeneity remained non-significant (p = 0.86), suggesting consistency in network effects across studies.

The analysis yields comparable results between common effect (OR: 2.88, 95% CI: 0.55–15.07) and random effects models (OR: 2.82, 95% CI: 0.54–14.82). Study weights are distributed across Reichenbach (2018) (23.6% common, 25.3% random), Kim (2023) (39.4% common, 25.4% random), and others, with several studies showing incomplete data. Individual odds ratios range from 0.86 to 6.43, though wide confidence intervals spanning the null value indicate no statistically significant network effects between experimental and control groups.

Conclusions

The meta-analysis examined the efficacy of various interventions targeting neuronal network degeneration in Alzheimer's disease through a systematic review of nine studies conducted between 2018 and 2024. The analysis focused on three key outcome measures: cognitive decline, neurodegeneration markers, and network integrity.

Significant trends in neural network degeneration across studies were found by our meta-analysis, especially in the relationship between network integrity and cognitive

impairment. According to the consensus results, compensatory mechanisms exist in the early stages of illness and are gradually undermined as pathology progresses. This is consistent with Wan's discovery of five different consensus clusters of transcriptional alterations and Jacobs' finding of dynamic changes in posterior cingulate cortex/precuneus function.

Key Findings:

Statistical analysis showed generally positive trends, though none achieved statistical significance across the measured outcomes. All three forest plots demonstrated odds ratios favoring experimental treatments (OR ≈ 2.7–2.9) but with wide confidence intervals crossing the null value. Minimal heterogeneity was observed across studies ($I^2 = 0\%$, $\tau^2 = 0$), suggesting consistency in findings despite varied intervention approaches.

Multiple promising therapeutic strategies emerged:

- Novel peptides (TAT-TrkB) showed potential in preventing BDNF receptor degradation.
- Immunometabolic regulation through hexokinase 2 targeting demonstrated reduction in neuroinflammatory markers.
- Cellular therapies, including human neural stem cells, showed promise in strengthening hippocampal networks.
- Receptor-based interventions (P2Y1 blockade, CB2 receptor agonists) demonstrated positive effects on network function.

Funnel plot analysis revealed symmetric distribution of studies, suggesting minimal publication bias. However, the small number of included studies (n = 9) limits definitive conclusions about publication bias.

Discussion

The findings suggest that while various therapeutic approaches show promise in addressing neuronal network degeneration in Alzheimer's disease, more robust evidence is needed to establish definitive efficacy. The consistent positive trends across different intervention types support continued investigation of multiple therapeutic approaches, particularly those targeting network integrity and neuronal function. The findings support the existence of compensatory mechanisms in early disease stages, which become progressively compromised as pathology advances.

The meta-analysis of therapeutic interventions across different modalities revealed consistent positive trends (OR ≈ 2.7–2.9) in improving network integrity and cognitive function, though statistical significance was not achieved. This pattern suggests that while current therapeutic approaches can influence neural network function, their individual effects may be insufficient to fully counteract the progressive nature of network degeneration in AD. Particularly encouraging were findings related to novel peptide therapies and immunometabolic regulation, which demonstrated notable effects on synaptic function and neuroinflammatory markers respectively. These results align with current understanding that AD pathology involves multiple cellular and molecular pathways affecting network integrity (Codocedo *et al.*, 2024, Kim *et al.*, 2023).

The relationship between therapeutic intervention and disease stage emerged as a critical factor. Studies targeting early-stage pathology, particularly those involving preventive approaches like TAT-TrkB peptide therapy and hexokinase 2 modulation, showed more promising outcomes in preserving network integrity. This temporal gradient in therapeutic efficacy suggests that early intervention, before significant network disruption occurs, may be crucial for treatment success. The findings parallel observations in other neurodegenerative conditions where early intervention has proven more effective in preserving neural network function (Fonseca-Gomes *et al.*, 2024).

An interesting pattern emerged in the analysis of cellular-based therapies, particularly those involving neural stem cells and activated macrophages. These approaches showed promise in strengthening hippocampal networks

and clearing pathological proteins, suggesting that cellular interventions might provide more comprehensive network restoration than single-target pharmacological approaches. However, the predominant use of mouse models in these studies highlights the need for careful translation to human applications (Codocedo *et al.*, 2024, Zhang *et al.*, 2019).

The role of receptor-based interventions, particularly P2Y1 receptor blockade and CB2 receptor agonism, demonstrated the potential importance of targeting specific signaling pathways in network preservation. These findings suggest that selective modulation of receptor systems might offer a more precise approach to maintaining network integrity while minimizing off-target effects. The consistency of positive trends across different receptor-targeting strategies suggests this may be a particularly promising avenue for future therapeutic development (Reichenbach *et al.*, 2018, Zhu *et al.*, 2023).

From a clinical perspective, these findings suggest that successful treatment of AD may require a paradigm shift toward earlier intervention and combined therapeutic approaches. The consistent positive trends across different intervention types, despite lacking statistical significance, suggest that current therapeutic strategies are on the right track but may need refinement and combination to achieve clinically meaningful outcomes.

We assessed a variety of treatment approaches, from innovative peptides to cellular therapies, despite the fact that included studies study contained fewer research and was mostly based on mice models. With odds ratios ranging from 2.7 to 2.9, the data indicated encouraging trends for a number of therapies; nonetheless, failed to reach statistical significance, underscoring the difficulties in converting therapeutic methods into successful treatments. However, The findings from Jacobs *et al.* (2013) and Wan *et al.* (2020) strongly complement our analysis by highlighting how neural network disruption occurs at multiple scales and through various mechanisms during disease progression (Jacobs *et al.,* 2013, Wan *et al.*, 2020).

Some limitations in our meta-analysis warrant consideration. Limitations included sample size variations and incomplete data reporting in several studies, predominant focus on mouse models limiting direct clinical applicability, relatively small number of included studies, and wide confidence intervals indicating substantial uncertainty in effect estimates.

Future research should focus on:

- Larger-scale studies with more standardized outcome measures.
- Investigation of combination therapies targeting multiple pathways.
- Translation of promising mouse model findings to human clinical trials.
- Development of more precise measurement tools for neuronal network integrity.
- Focus on early intervention strategies to preserve network function before significant degeneration occurs.

The meta-analysis highlights the complexity of treating Alzheimer's disease and suggests that a multi-faceted approach targeting various aspects of neuronal network degeneration may be necessary for effective treatment. While current interventions show promise, further research with larger sample sizes and more standardized methodologies is needed to establish definitive therapeutic recommendations. Our meta-analysis reveals promising trends in therapeutic approaches to combat neuronal network degeneration in AD, it also highlights the need for more comprehensive, early-stage interventions and standardized research methodologies. The complexity of AD's impact on neural networks suggests that successful treatment strategies will likely require multiple, complementary approaches targeting different aspects of network preservation and restoration.

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REVIEW ARTICLE

ADVANCES IN ANESTHESIOLOGY APPLIED DURING THE SURGICAL SCOLIOSIS CORRECTION. A NARRATIVE REVIEW

POSTĘPY W ANESTEZJOLOGII STOSOWANEJ PODCZAS CHIRURGICZNEJ KOREKCJI SKOLIOZY. PRZEGLĄD NARRACYJNY

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ABSTRACT
Scoliosis surgery, particularly in adolescent idiopathic scoliosis, necessitates careful anesthetic management to optimize surgical outcomes and minimize neurophysiological compromise. Neurophysiological compromise refers to the potential disruption of somatosensory-evoked potentials (SSEPs) and motor-evoked potentials (MEPs) during surgery, which are critical indicators of spinal cord integrity. Preserving these signals is essential to reduce the risk of intraoperative neurological injury, such as motor or sensory deficits. This narrative review presents current anesthetic techniques, focusing on Total Intravenous Anesthesia (TIVA) and inhalational methods and their implications for intraoperative neurophysiological monitoring and postoperative recovery. TIVA, utilizing agents like propofol and remifentanil, has emerged as a preferred approach due to its favourable pharmacodynamics, resulting in less suppression of SSEPs and MEPs than inhalational agents. The review highlights the potential of adjuncts, including dexmedetomidine and low-dose ketamine, in enhancing analgesia and mitigating opioid-related side effects.

Furthermore, the erector spinae plane (ESP) block is discussed as an innovative regional technique that may improve postoperative pain control while reducing systemic opioid requirements. Emphasizing a multimodal analgesic strategy, the review underscores the importance of integrating various pharmacological and non-pharmacological approaches to optimize postoperative pain management. Ongoing research is vital for refining anesthetic protocols and enhancing patient outcomes in scoliosis surgery, ultimately ensuring the safety and efficacy of these complex procedures.

Keywords: surgery, anaesthesia, scoliosis

STRESZCZENIE
Operacja skoliozy, szczególnie w przypadku młodzieńczej skoliozy idiopatycznej, wymaga starannego zarządzania anestezjologicznego w celu optymalizacji wyników chirurgicznych i minimalizacji ryzyka uszkodzenia neurofizjologicznego. Niniejszy przegląd narracyjny analizuje aktualne techniki anestezji, koncentrując się na całkowitej anestezji dożylnej (TIVA) oraz metodach wziewnych i ich wpływie na śródoperacyjne monitorowanie neurofizjologiczne oraz powrót do zdrowia po operacji. TIVA, z wykorzystaniem takich leków jak propofol i remifentanyl, zyskała na popularności ze względu na korzystne działanie farmakodynamiczne, które skutkuje mniejszym hamowaniem potencjałów wywołanych somatosensorycznych i motorycznych w porównaniu z lekami wziewnymi. Przegląd podkreśla również potencjał

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adiuwantów, takich jak deksmedetomidyna i ketamina w małych dawkach, w poprawie analgezji i redukcji działań niepożądanych związanych z opioidami. Ponadto, omawiany jest blok płaszczyzny mięśnia prostownika grzbietu (ESP) jako innowacyjna technika regionalna, która może poprawić kontrolę bólu pooperacyjnego, zmniejszając jednocześnie zapotrzebowanie na opioidy systemowe. Zwracając uwagę na strategię multimodalnego zarządzania bólem, przegląd podkreśla znaczenie integracji różnych podejść farmakologicznych i niefarmakologicznych w celu optymalizacji leczenia bólu pooperacyjnego. Kontynuacja badań jest kluczowa dla dalszego doskonalenia protokołów anestezjologicznych oraz poprawy wyników leczenia pacjentów poddawanych operacji skoliozy, zapewniając ostatecznie bezpieczeństwo i skuteczność tych złożonych zabiegów.

Słowa kluczowe: znieczulenie, chirurgia, skolioza

Introduction

Scoliosis surgery, particularly in adolescent idiopathic scoliosis, is a complex procedure to correct abnormal spinal curvature while preserving or improving spinal cord function (Antolovich *et al.,* 2022). Given the intricate relationship between anesthetic techniques and neurophysiological outcomes, the selection of anesthesia is critical for optimizing surgical success and patient safety (Domagalska *et al.,* 2023). The dual objectives of providing adequate analgesia while minimizing the potential for neurophysiological compromise necessitate a thorough understanding of the anesthetic agents and techniques available (Antolovich *et al.,* 2022). Neurophysiological compromise in the context of scoliosis surgery refers to the potential disruption of intraoperative neurophysiological monitoring signals, such as somatosensory-evoked potentials (SSEPs) and motor-evoked potentials (MEPs), which are critical for assessing spinal cord integrity during surgery (Rao *et al.,* 2021). Specific anesthetic agents can suppress or alter these signals, making detecting intraoperative neurological injury in real-time challenging (Grasso *et al.,* 2021). For instance, inhalational anesthetics and high doses of specific intravenous agents may significantly diminish the amplitude or prolong the latency of these signals, increasing the risk of missing subtle signs of spinal cord compromise (Ma *et al.,* 2023). Therefore, anesthetic strategies must balance providing effective pain relief and hemodynamic stability while preserving the reliability of neurophysiological monitoring to ensure patient safety. This review examines the current landscape of anesthetic practices in scoliosis surgery, emphasizing their implications for intraoperative monitoring, recovery, and postoperative pain management (Chmielewska *et al.,* 2020).

Anesthetic Techniques

1. Total Intravenous Anesthesia (TIVA)

Total intravenous anesthesia (TIVA), commonly employing agents such as propofol and remifentanil, has become increasingly favored in scoliosis surgeries due to its favorable pharmacodynamic properties (Petre *et al.,* 2021). Propofol, an alkyl phenol derivative, is known for its rapid onset and short duration of action, making it ideal for maintaining a stable anesthesia depth. Studies indicate that TIVA leads to less suppression of somatosensory evoked potentials (SSEPs) and motor-evoked potentials (MEPs) compared to inhalational agents, particularly nitrous oxide, which has been s, shown to impair alpha motor neuron excitability significantly (Deguchi *et al.,* 2021).

When combined with remifentanil, propofol facilitates rapid recovery and minimizes dose-dependent alterations in neurophysiological monitoring. It provides a reliable platform for continuous assessment of spinal cord function during surgery (Yang *et al.*, 2022).

Research indicates that TIVA results in a lower incidence of intraoperative hypotension and enhances recovery profiles, allowing for quicker emergence from anesthesia and improved neurological assessments in the postoperative period.

2. Inhalational Anesthesia

Inhalational anesthetics, including halogenated agents (e.g., sevoflurane and isoflurane) and nitrous oxide, remain widely used in various surgical settings; however, their application in scoliosis surgery is contentious due to their neurophysiological effects (Li *et al.*, 2020). Inhaled anesthetics are known to produce dose-dependent reductions in MEP amplitudes, raising concerns about their suitability in procedures requiring meticulous spinal cord integrity monitoring. Nitrous oxide has been implicated in impairing neuromuscular transmission and alpha motor neuron excitability, leading to significant reductions in MEP recordings (Badenes *et al.*, 2021).

Although inhalational anesthesia offers advantages in terms of ease of administration and rapid titration, its potential to disrupt neurophysiological monitoring necessitates careful consideration, particularly in surgeries where spinal cord integrity is paramount.

3. Combination Approaches

Combining various anesthetic techniques can enhance outcomes in scoliosis surgery. For instance, adjuncts such as dexmedetomidine, an alpha-2 adrenergic agonist, can be utilized for sedation and analgesia without causing respiratory depression (Walker *et al.*, 2020). Dexmedetomidine has been shown to improve conditions for intraoperative neurophysiological monitoring while maintaining hemodynamic stability (Pacreu *et al.*, 2021). Moreover, the intraoperative infusion of low-dose ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been suggested to attenuate remifentanil-induced hyperalgesia and opioid tolerance, thereby reducing postoperative opioid requirements (Walker *et al.*, 2020).

4. Erector Spinae Plane Block

The erector spinae plane (ESP) block is an emerging regional anesthesia technique that has gained attention in the context of thoracic and lumbar surgeries, including scoliosis correction (Domagalska *et al.*, 2023). This block involves injecting a local anesthetic into the plane between the erector spinae muscle and the vertebral fascia, providing analgesia to the dermatomes supplied by the spinal nerves (Domagalska *et al.*, 2024). The ESP block exerts its effect through molecular and biochemical mechanisms. By delivering local anesthetics into the fascial plane deep to the erector spinae muscle, the block results in the diffusion of the anesthetic agent to paravertebral spaces, affecting both the dorsal and ventral rami of spinal nerves (Holland *et al.*, 2022; Apaydın Abstracts of the 20th Congress of the IFAA). This action inhibits sodium ion channels on neuronal membranes, preventing depolarization and subsequent transmission of pain signals (Chin *et al.*, 2021). Additionally, the ESP block may reduce local inflammation by stabilizing mast cells and decreasing the release of pro-inflammatory mediators like histamine and cytokines (Domagalska *et al.*, 2024, Jinn *et al.*, 2021; Liu *et al.*, 2021; Tantri *et al.*, 2023). This dual mechanism contributes to adequate analgesia and mitigating the neuroinflammatory response, enhancing postoperative recovery (Reysner *et al.*, 2024).

The ESP block has shown promise in reducing postoperative pain and opioid consumption in patients undergoing various thoracic and abdominal procedures (Domagalska *et al.*, 2023b). Preliminary studies indicate that the ESP block can enhance analgesic efficacy while minimizing the need for systemic opioids, which may help mitigate the risks of opioid-related side effects and hyperalgesia (Domagalska *et al.*, 2024). Additionally, its application in scoliosis surgery may improve intraoperative conditions by allowing for better patient positioning and minimizing intraoperative movement, thereby supporting effective neurophysiological monitoring.

Neurophysiological monitoring

Intraoperative neurophysiological monitoring is essential in scoliosis surgery to detect potential spinal cord ischemia or injury (Daroszewski *et al.,* 2023). SSEPs and MEPs are the primary modalities for evaluating spinal cord function and integrity (Daroszewski *et al.,* 2023b). The anesthetic technique can significantly influence these recordings, with TIVA often yielding more stable results than inhalational agents (Thakkar *et al.,* 2023). Maintaining SSEP and MEP amplitudes within acceptable limits is crucial for real-time assessments of spinal cord status (Castellanos *et al.,* 2020). If significant changes in neurophysiological signals are observed, the ability to perform rapid wake-up tests is essential for validating these findings and making timely surgical adjustments if necessary.

Recovery profiles

The recovery profile from anesthesia is critical to scoliosis surgery, influencing both immediate postoperative outcomes and long-term recovery (Rao *et al.,* 2021). Compared to inhalational agents, TIVA is associated with faster recovery times, a quicker onset of spontaneous ventilation, and earlier neurological assessments (Grasso *et al.*, 2021). Studies have demonstrated that patients receiving TIVA require less time to return to baseline neurologic function, facilitating optimal conditions for postoperative monitoring and evaluation of spinal cord integrity (Spitzer *et al.*, 2022).

In contrast, inhalational anesthetics can prolong recovery times, delaying the return of motor function and potentially complicating postoperative assessments (Kawaguchi *et al.,* 2020). A rapid recovery is particularly beneficial for patients undergoing neurophysiological monitoring, as it allows for timely evaluation of spinal cord function post-surgery (Tanaka *et al.*, 2024).

Postoperative pain management

Effective postoperative pain management is paramount in enhancing recovery and minimizing complications following scoliosis surgery (Lee *et al.,* 2020). A multimodal analgesic approach, integrating . Various pharmacological and non-pharmacological strategies to address pain from multiple pathways are increasingly regarded as the best practice (Collins *et al.,* 2015).

1. Opioid Use and Alternatives

Opioids remain a cornerstone of postoperative pain management; however, their associated side effects, including respiratory depression, constipation, and potential for addiction, highlight the need for alternative analgesic strategies (Shah *et al.,* 2020). The administration of gabapentin, an anticonvulsant agent with analgesic properties, pre- and postoperatively, has been shown to significantly reduce opioid consumption and improve pain scores in patients undergoing scoliosis surgery (Anderson *et al.,* 2020). Additionally, intravenous acetaminophen is effective in enhancing analgesia while minimizing the adverse effects commonly associated with NSAIDs and opioids (Murdock *et al.,* 2023).

2. Regional Anesthesia

Regional anesthesia techniques, including epidural and intrathecal analgesia, have shown promise in providing effective postoperative pain relief while reducing systemic opioid exposure (Setijanto *et al.*). Evidence suggests that epidural analgesia, particularly with local anesthetics or a combination of local anesthetics and opioids, can significantly improve postoperative pain control and enhance patient satisfaction (Chin *et al.,* 2017). However, the efficacy of these techniques remains a subject of debate, as some studies have reported no significant differences in outcomes compared to systemic analgesia alone.

The incorporation of the ESP block into postoperative pain management protocols may further improve outcomes by reducing the reliance on systemic opioids and enhancing overall patient satisfaction (Domagalska *et al.*, 2024; Domagalska *et al.*, 2023). The ESP block offers several advantages in avoiding deep anesthesia during scoliosis

surgery. By providing adequate regional analgesia, the ESB reduces the reliance on high doses of systemic opioids and general anesthetic agents, which are often required to achieve adequate pain control (Domagalska *et al.,* 2023). This allows for lighter planes of anesthesia, preserving the integrity of intraoperative neurophysiological monitoring signals, such as SSEPs and MEPs, critical for detecting spinal cord function during scoliosis surgery (Domagalska *et al.*, 2024). Moreover, the ESP block's opioid-sparing effect minimizes the risk of respiratory depression and hemodynamic instability, ensuring smoother perioperative management (Jinn *et al.,* 2021).

Feedback from surgeons regarding the use of ESP block has mainly been positive. Many reports that lighter anesthesia facilitates more precise and more stable neuromonitoring recordings, which enhances surgical precision and safety (Domagalska *et al.,* 2024). Surgeons also appreciate the reduction in postoperative opioid-related complications, such as nausea, sedation, and delayed recovery, which allows for improved patient outcomes and faster mobilization (Fung *et al.,* 2023). These advantages make ESP block a valuable component of multimodal analgesia in scoliosis surgery, aligning well with both anesthetic and surgical goals.

Conclusion

Anesthesia for scoliosis surgery encompasses diverse techniques, each with unique implications for intraoperative monitoring and postoperative recovery. TIVA is increasingly favored for its stability in neurophysiological monitoring and rapid recovery profiles. At the same time, inhalational agents are approached with caution due to their potential adverse effects on spinal cord function. A multimodal approach to postoperative analgesia is essential for effective pain management, focusing on reducing opioid use and enhancing patient outcomes. The application of regional techniques, such as the erector spinae plane block, holds promise for further improving postoperative pain control and reducing systemic opioid consumption.

As our understanding of the interaction between anesthesia and spinal cord function evolves, ongoing research is crucial for optimizing anesthetic practices in scoliosis surgery. Future studies should aim to elucidate the most effective anesthetic regimens, assess long-term outcomes, and explore novel adjunctive therapies that enhance analgesia while minimizing adverse effects. This comprehensive understanding will ultimately improve care and outcomes for patients undergoing scoliosis correction procedures.

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REVIEW ARTICLE

NON-PHARMACOLOGICAL TREATMENT METHODS FOR DEPRESSIVE DISORDER: A SYSTEMATIC REVIEW

NIEFARMAKOLOGICZNE METODY LECZENIA DLA ZABURZEŃ DEPRESYJNYCH

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ABSTRACT
Depressive disorder is a widespread psychological condition. It affects approximately 5% of adults globally. Untreated depression can compromise the quality of life in all its aspects, leading to deterioration of physical health or even suicide. Currently, the recommended treatment is pharmacological therapy, however, not all patients respond to traditional methods, and drug treatment is related to many undesirable side effects. While antidepressants remain the gold standard, non-pharmacological treatment methods are gaining popularity and recognition in Western medicine. While these methods are not always available as a substitute for pharmacotherapy, they can complement and enhance the therapeutic effects. In this paper, we will cover the newly researched, holistic methods of non-pharmacological treatment of depression, including physical exercise, dietary adjustments, psychedelics, or mindfulness, as well as the commonly accepted techniques, such as psychotherapy, electroconvulsive therapy, or deep brain stimulation. This review aims to present alternative treatments for depression and offer insight into the complex topic of improving quality of life and obtaining general well-being.

Keywords: depression, depression treatment, depressive disorder, non-pharmacological treatment of depression, depression management

STRESZCZENIE
Depresja jest szeroko rozpowszechnionym zaburzeniem psychicznym. Dotyka około 5% dorosłych na całym świecie. Nieleczona depresja może pogorszyć jakość życia we wszystkich jego aspektach, prowadząc do pogorszenia zdrowia fizycznego, a nawet samobójstwa. Obecnie zalecanym leczeniem jest terapia farmakologiczna, jednak nie wszyscy pacjenci reagują na tradycyjne metody, a leczenie farmakologiczne wiąże się z wieloma niepożądanymi skutkami. ubocznymi. Podczas gdy leki przeciwdepresyjne pozostają złotym standardem, niefarmakologiczne metody leczenia zyskują coraz większą popularność i uznanie w zachodniej medycynie.

Chociaż metody te nie zawsze są dostępne jako substytut farmakoterapii, mogą one uzupełniać i wzmacniać efekty terapeutyczne. W niniejszym artykule, omówimy nowo zbadane, holistyczne metody niefarmakologicznego leczenia depresji, w tym ćwiczenia fizyczne, dostosowanie diety, psychodeliki lub uważność, jak również powszechnie akceptowane techniki, takie jak psychoterapia, terapia elektrowstrząsowa czy głęboka stymulacja mózgu.

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Niniejszy przegląd ma na celu przedstawienie alternatywnych metod leczenia depresji i zaoferowanie wglądu w złożony temat poprawy jakości życia i uzyskania ogólnego dobrostanu.

Słowa kluczowe: depresja, leczenie depresji, zaburzenie depresyjne, niefarmakologiczne leczenie depresji, zarządzanie depresją

Introduction

Depressive disorder also known as depression is a common psychiatric disorder which includes symptoms such as low mood, loss of energy, problems with sleeping, suicidal thoughts and reluctance to perform daily activities. Depressive episodes which last for at least two weeks differ from regular mood changes or grief periods and significantly reduce the quality of life. Depression has a major influence on both personal life and work environment due to visible lack of pleasure and interest in undertaking new or familiar activities.

The factors which contribute to becoming depressed have biological, psychological and social background. Though some people for example victims of sexual abuse or people suffering a bereavement are more likely to fall into depression, it can betide anyone.

It is estimated that worldwide 3.8% of the population that is approximately 280 million people suffer from depression. There is a higher percentage of depressed women (6%) and slightly lower of depressed men (4%). Depression can ultimately lead to suicide and is responsible more than 700 000 deaths every year (Depressive Disorder (Depression), no date).

Aim

The aim of this systematic review is to explore unstandardized methods of depression treatment since 10–30% of patients are drug-resistant. Moreover, 63% of depression patients don't respond well to pharmacological treatment and the prevalence of side effects is high. This paper comprehensively analyses the approved non-pharmacological treatment methods as well as the alternative approaches as they have gained importance in terms of social and cognitive aspects.

Materials and methods

This systematic review paper was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The eligibility criteria were as follows. We included studies that investigated non-pharmacological treatments for depressive disorder, irrespective of the patients' nationality, age (adolescents, adults, elderly), or gender. Inclusion of all groups underlined the importance of assessing success rates for all non-pharmacological treatment methods mentioned as depression is a widespread disease. To ensure the review captured a broad range of approaches, studies using both human and animal models were considered. Animal studies were considered only if they were used to test the efficacy of certain non-pharmacological depression treatments. The inclusion criteria specified that only publications in English or Polish were eligible. Types of works chosen included: meta-analyses, reviews, systematic reviews, books, guidelines. Case reports were excluded from the selection criteria. Works were primarily chosen according to their title and/ or abstract. Then, an in-depth analysis of full text or certain sections was made by each member of the team. No tools were used for text screening. Initially, a 5-year publication window (2019 onwards) was applied, but due to the established nature of certain treatments (e.g., TMS, ECT), earlier studies were also included (*1967, 1977, 1985, 1995, 1997, 1998, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018*). This allowed for a comprehensive examination of both recent advancements and foundational research. Only published manuscripts were eligible for inclusion. The search strategy included

finding sources in *PubMed* and *Google Scholar*. These databases were chosen as they serve as reliable sources of medical knowledge. Additionally, a scientific journal *Psychiatria Polska* was searched through as it provides valuable knowledge in the field of psychiatry. All sources chosen provide insightful pieces of knowledge about non-pharmacological treatment methods for depressive disorder. As the scope of our systematic review is broad, many different papers researching various topics had to be used. All databases were searched manually by 5 independent people. After initial screenings, the final selection was discussed and agreed upon by the entire research team to ensure consistency and thoroughness. No software was used to aid with the data collection process.

Results

1. Approved Non-pharmacological Treatment Methods

Electroconvulsive therapy

Electroconvulsive therapy (ECT) is widely recognized as one of the most effective treatments for psychological disorders. It is used to treat depression, schizophrenia, bipolar manic states, schizoaffective disorder, schizophreniform disorder, and catatonia. (Kellner *et al.* 2012). Its efficiency has been proven through multiple studies, (Rosenquist *et al.* 2018; Lex *et al.* 2021) and it has remained one of the most powerful tools in depression management, despite the cultural stigma. ECT originated in the 20th century and the principles of this technique have not been significantly modified since (Leiknes *et al.* 2012). ECT is based on brain stimulation treatment, achieved by applying an electrical charge through the brain to induce a seizure lasting around 30 seconds (Kirov *et al.* 2021). The procedure is conducted under controlled clinical conditions, using general anesthesia along with muscle relaxants. The recommended duration of the treatment is 6–12 sessions, scheduled two or three times per week, although these numbers can be adjusted depending on the severity of the case (Thirthalli *et al.* 2020). Research on the molecular level has provided insight into the mechanism of ECT, with the formation of several theories on the basis of action. The monoamine neurotransmitter theory suggests that ECT works by increasing the levels of serotonin and norepinephrine, which improves neurotransmission and provides an antidepressive effect (Youssef *et al.* 2018). The neuroendocrine theory entails the effect of pituitary and hypothalamic hormones, which are released upon brain stimulation. The anticonvulsant theory ties ECT effectiveness to its anticonvulsant nature. This statement could be supported by the fact that there has been noted an increase in seizure threshold and decrease in seizure duration, as the treatment progresses (Kellner *et al.* 2012). The neurotrophic theory suggests that ECT enhances neurogenesis and neurotrophic signaling in the brain, which has been proven by a recording of raised levels of neurotrophic factors, both in animals and humans (Takamiya *et al.* 2017). Despite its effectiveness, ECT does involve risk. Seizures, although controlled, can negatively impact the function of cardiovascular, pulmonary, and central nervous system, therefore testing is needed before initiating the treatment (Kellner *et al.* 2012). The most dangerous side effect of ECT is impairment of cognitive function and memory loss. These deficits can vary in severity and duration, and they can negatively impact quality of life (Lex *et al.* 2021; Kirov *et al.* 2021). Research has proven that adjusting the frequency and intensity of treatments can mitigate the negative effects (Thrithalli *et al.* 2020). While the side effects could lead to deterioration of general health, ECT is a great solution, especially for patients dealing with treatment-resistant depression. In a meta-analysis of 34 studies, the calculated response rate reached 60.5% and a remission rate of 47.8% (Van Diermen *et al.* 2018).

Psychotherapy

Psychotherapy has become the officially accepted non-pharmacological treatment for depression. It is believed that the effectiveness of psychotherapy for personality

disorders, anxiety or depression is comparable to the effect of drug treatment (Olano *et al.* 2022). The exception is severe depression, in which drug treatment in combination with psychotherapy has better results. There are many types of psychotherapy, (Wienicke *et al.* 2023) they are behavioral-cognitive, psychoanalytic, existential-humanistic, systemic and psychodynamic therapy. Each type of psychotherapy focuses on different parts of the complex picture of the patient's psychosocial and personality problems. The choice of therapy is individual, depending on the needs and preferences of the patient. Patients diagnosed with depression are most often referred to psychodynamic therapy or behavioral-cognitive therapy. Psychodynamic therapy (Pearce *et al.* 2022) is based on the principle of an interpretive and supportive continuum (Ribeiro *et al.* 2017; Porcelan and Scribner 2022). Interpretive interventions allow the patient to gain insight into his behavior and reduce the repetition of his problems. Provisional insight enhancement intervention is an interpretive intervention that makes unconscious impulses, defense mechanisms (Ribeiro *et al.* 2017) and wishes conscious. Reinforcement intervention involves strengthening abilities that are unavailable to the patient as a result of acute stress, (Porcelan and Scribner 2022) or have not been fully developed. Psychodynamic psychotherapy allows patients to better understand themselves, their behavior and emotions. As a result, patients become more aware of their actions and the decisions they make. It also affects the formation of relationships with other people. This happens thanks to the transfer of what lies in the human unconscious into consciousness. Depending on the patient's condition, a distinction is made among psychodynamic therapy, short-term therapy lasting up to 25 sessions and long-term therapy, which is better at preventing relapse. An extremely important aspect is the patient's relationship with the therapist, as this is the only way to see the unaware patient. In psychodynamic psychotherapy, an important point is the phenomenon of transference; that is, the identification of the therapist with a close person in whose life the patient had confidence. Then all gestures and words of the therapist are associated with this imagined person, which triggers various emotions in the patient. These emotions are a starting point and can lead to changes in how the patient feels about other relationships. There are many empirical studies that support the effectiveness of psychodynamic therapy (Ribeiro *et al.* 2017). A growing body of evidence shows that the positive changes achieved intensify after therapy ends. On the other hand, it is not a healing modality for everyone, (Olano and Rosenbaum 2022) as many do not improve or achieve only limited effect. Brief psychodynamic therapy is implemented when five criteria are met: limited time, limited goals, maintaining focus, high therapist involvement (Porcelan and Scribner 2022) and rapid intervention. Because of the limited therapy time, the therapist should adapt and overcome unforeseen challenges and quickly build a relationship with the patient. During the session, the therapist should take the right attitude towards therapy. It should be remembered that the patient-therapist relationship is extremely important during therapy and should be a priority during treatment. Despite the many controversies about psychodynamic therapy, (Ribeiro *et al.* 2017) its impact on the treatment of depression is growing. The effectiveness of psychodynamic therapy in the treatment of depression is comparable to that achieved in drug treatment (Olano and Rosenbaum 2022). Behavioral-cognitive therapy is the best researched therapeutic strategy for any mental disorder. It has been confirmed by a very large number of studies. The effectiveness of this type of therapy is equal or even greater compared to pharmacotherapy. It is believed to result in a more durable response compared to drug therapy (Sudak 2011; Gautam *et al.* 2020) and may protect against relapse. The therapeutic

concept of behavioral-cognitive coping with depression consists of three stages: focusing on automatic thoughts, depressogenic cognitive styles, and focusing on the way the person relates to others; and the behavioral changes necessary to enable the individual to move out of the problematic situation (Powell *et al.* 2008). An important aspect of therapy, as in psychodynamic therapy, is the relationship between patient and therapist. The therapist acts as a teacher, working together with the patient to achieve the therapy goal and functional thinking, which should result in positive reinforcement and social interactions (Powell *et al.* 2008; Sudak 2011). The facilitator aims to change behavior, which is likely to improve the patient's mood, appetite or sleep quality. Because of patients' memory problems and slowed thinking, therapy includes summarizing important points discovered during sessions. An important component of behavioral-cognitive therapy is behavioral activation (Sudak 2011). Its main goal of enabling patients to cope with negative symptoms. These strategies focus on engaging the patient, obtaining relevant information for therapy and alleviating symptoms. They are individualized (Powell *et al.* 2008) for each patient. Another benefit of behavioral activation is the restoration of the patient's correct thought patterns, which are associated with withdrawal and avoidance. Patients think that life has no meaning, they have no energy, they are afraid to take risks for fear of failure. In this case, it is very important for the therapist to instruct the patient and help him or her engage in the activity. When the patient has been given behavioral activation, the therapist emphasizes the cognitive aspect. This helps patients change the beliefs and behaviors that trigger a certain state (Sudak 2011) and identify automatic thoughts. A very important advantage of cognitive therapy is that the patient is active in his own treatment. This involves the patient finding negative thoughts on his own and seeking alternatives for them. He finds distorted perceptions and learns about the factors that contribute to the maintenance of depressive behavior (Powell *et al.* 2008). Cognitive-behavioral therapy is usually associated with 'homework', Patients are assigned tasks to complete outside of sessions. This is because the essence of learning new skills is practice and must be repeated (Chen *et al.* 2009) before they are automatically accepted. It has been proven that patients who use skills learned during therapy are less likely to relapse. About 70 percent of mental disorders already surface before the age of 25 and, if not treated effectively, can progress to a chronic state. People between the ages of 18 and 25 are much more likely to suffer from mental health disorders, as they are more likely to become addicted to psychoactive substances (Ritivo *et al.* 2021) and have suicidal thoughts. The online communication skills of adolescents have been used in treatment, where they can take classes to treat depressive disorders. A randomized controlled trial was conducted comparing behavioral-cognitive therapy combined with standard psychiatric care in adolescents taking place online versus conventional psychiatric care in adolescents aged 18–30 with diagnosed depressive disorders (Ritivo *et al.* 2021). All participants received classical psychiatric care, that is, one session per month, while participants in the experimental group received an additional intervention consisting of online software. The results obtained confirm that adolescent depression (Ritivo *et al.* 2021) can be effectively treated with online software therapy. This means that all possible and proven therapies must be used so that as many patients as possible have the opportunity to recover from depression.

Vagus nerve stimulation

Stimulation of the cervical vagus nerve to treat brain diseases is supported by both anatomical and functional traits. The vagus nerve contains both sensory afferent fibers and efferent motor fibers. The visceromotor efferent fibers originate in the dorsal motor

nucleus of the medulla, while the sensory afferent fibers terminate in the nucleus tractus solitarius (NTS), also in the medulla.

This dual structure allows vagus nerve stimulation (VNS) to impact on various regions and functions in the brain. Afferent fibers carry sensory information to the brain. They also influence brainstem nuclei and higher brain structures. Different fibers regulate autonomic functions, such as heart rate, lung function, and digestion. By these functions they indirectly affect brain activity. Therefore, stimulating the cervical vagus nerve can potentially treat neurological afflictions like epilepsy, depression, and inflammatory brain diseases by leveraging these pathways.

The afferent fibers of the vagus nerve use neurotransmitters such as substance P, calcitonin gene-related peptide and the excitatory amino acid L-glutamate. The nucleus tractus solitarius (NTS) projects to several key areas:

- Medullary motor nuclei.
- Structures in midbrain: locus coeruleus (LC), dorsal raphe nucleus (DRN), brainstem interneurons and parabrachial nucleus (PBN).
- Forebrain regions such as the hypothalamus, amygdala, bed nucleus of the stria terminalis (BNST), and insular cortex.
- What is more, nuclei like the LC and DRN project to limbic forebrain regions.

Thus, brain areas implicated in depression-related behaviors are innervated directly or indirectly, by projections from afferent vagal fibers terminating in the NTS.

The procedure of Vagus Nerve Stimulation (VNS) involves implanting a stimulation generator which is connected to bipolar electrodes. They are positioned around the left vagus nerve. Stimulation of the left vagus nerve, rather than the right, is preferred because of the less impact on heart rate. This is used for treating conditions like treatment-resistant depression (TRD) or epilepsy. The left vagus nerve innervates the atrioventricular node (AV). In contrast, the right vagus nerve innervates the sinoatrial (SA) node, which has a more significant effect on heart rate. Stimulation of the vagus nerves affects heart rate according to these specific innervations. The bipolar stimulating electrode contains the cathode at the proximal lead and the anode at the distal lead. This type of arrangement simplifies action potential propagation towards the central nervous system by creating an anodal block at the distal lead.

In 2000, Elger *et al.* were the firsts who observed improvement of mood in patients with epilepsy. It was irrespective of their seizure reduction. This study employed a double-blind, randomized comparison to measure the effects of various VNS doses without any control group (sham stimulation). Despite the fact that the high doses were less tolerated, 70% to 75% of patients in this group reached their assigned dose. Comparable efficacy was noted across all three dose groups. Following a 22-week treatment period, response rates ranged from 10% to 20% in the low-dose group and 19% to 31% in the high-dose group. Continued behavioral enhancement was observed over time, with 25% of non-responders at 22 weeks exhibiting a response at 50 weeks. Notably, responders at 22 weeks, particularly those receiving medium or high doses, sustained their response up to 50 weeks. The low-strength/high-frequency group demonstrated superior outcomes. Additional prospective studies are warranted, especially because of the evidence suggesting frequency-dependent effects of VNS in patients. The results can be provided by functional magnetic resonance imaging (fMRI) findings (Carreno and Frazer 2017).

Single clinical observations of improved mood in patients with epilepsy, even in the absence of better seizure control after VNS implantation, led to a pilot prospective study of the effect of VNS on mood in epilepsy patients treated with a VNS device or antiepileptic drugs. In the VNS group, there was a significant improvement in mood at three months that appeared independent of any improvement in seizure control, suggesting that VNS had a distinct effect on depressive symptoms. The same finding was reported independently in a European study conducted

around the same time in a group of patients with epilepsy (n = 11) with mild depression (O'Reardon *et al.* 2006).

However, despite promising efficacy in treating depression, the surgical risks, high costs of the procedure and potential side effects make it less attractive and restrict access. (Ventureyra 2000; Fitzgerald 2013). To overcome these barriers to the use of invasive VNS (iVNS), a non-invasive method of transcutaneous vagus nerve stimulation (taVNS) has been developed that is attracting more and more attention.

taVNS

Transcutaneous auricular vagus nerve stimulation (taVNS) by emphasizing its anatomical and functional impacts on the brain can be used as a therapy for depression. The research which was made by Peuker and Filler (Peuker and Filler 2002) identified that specific areas of the ear, such as the shells and tragus, are innervated by the auricular branch of the vagus nerve (ABVN).

This branch has significant neural projections to the solitary tract nucleus, which connects to extensive regions of the brain that are involved in depression (Badran *et al.* 2018; Butt *et al.* 2020).

Notably, taVNS has been shown to influence these brain regions similarly to invasive vagus nerve stimulation (iVNS).

Research indicates that taVNS can modulate activity in areas such as the orbitofrontal cortex, anterior cingulate cortex (ACC), dorsolateral prefrontal cortex, superior and medial frontal cortex, temporal cortex, parietal area, hemi frontal nucleus, and amygdala. These regions play essential roles in mood regulation and they are involved in onset of depression (Rush *et al.* 2005; Conway *et al.* 2006; Kraus *et al.* 2007; Dietrich *et al.* 2008; Kosel *et al.* 2011; Frangos *et al.* 2015; Kaczmarczyk *et al.* 2021).

Thus, the modulation of these brain areas through taVNS suggests its potential as a non-invasive therapeutic option for depression, offering similar benefits to classical iVNS without the need for surgical implantation.

Based on the findings of meta-analysis 'The efficacy and safety of transcutaneous auricular vagus nerve stimulation in the treatment of depressive disorder: A systematic review and meta-analysis of randomized controlled trials' it can be inferred that transcutaneous auricular vagus nerve stimulation (taVNS) has an effective and safe therapeutic effect from mild to moderate depression with comparable efficacy to antidepressants. Nevertheless, it is imperative for practitioners and healthcare providers to exercise prudence in interpreting these results, because of low to very low quality of evidence. To establish a more robust foundation for the efficacy of taVNS across different types and severity levels of depression, further multicenter double-blinded randomized controlled trials (RCTs) are warranted. These studies are essential for enhancing the quality of evidence and providing more conclusive insights into the therapeutic potential of taVNS in depression management (Tan *et al.* 2023).

Transcranial magnetic stimulation

Transcranial Magnetic Stimulation (TMS) is a non-invasive method used in neurology since 1985 (Tan *et al.* 2023). It is considered as one of the alternative methods for treatment-resistant depression (TRD) and has been approved by the Health Canada, U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH) (Barker *et al.* 1985). What is unique about TMS, amongst methods such as Vagus Nerve Stimulation or Electro convulsions, is that the procedure does not interrupt with the skull structure and is performed with a full consciousness of the patient (Holtzheimer *et al.* 2014).

Over the years, several TMS methods have been developed, one example is the Repetitive TMS (rTMS). rTMS is a method that involves multiple signals over a short period of time [39]. International clinical trials proved safety and efficacy of rTMS which allowed for implementation of this method as an alternative for pharmacotherapy in TRD (George *et al.* 1995; Janicak *et al.* 2008; George *et al.* 2010).

It usually targets the Dorsolateral Prefrontal Cortex (DLPFC) of the left hemisphere (Koutsomitros *et al.* 2021) and it can depolarize or hyperpolarize certain cortical neurons (George *et al.* 1995). In the procedure, an electromagnetic coil is placed on a patient's scalp and short, but powerful (0.5–2 Tesla) magnetic fields are provided. They penetrate to the cortex inducing an electric current in neurons (Holtzheimer *et al.* 2014). Coils used in rTMS vary in shape and can be planar, helmets or figures of eight (De Risio *et al.* 2020). Additionally, various intensity and duration can be applied, but usually 10 Hz frequency is used over (Holtzheimer *et al.* 2014; Kim *et al.* 2016; Koutsomitros *et al.* 2021) weeks in daily sessions (Perera *et al.* 2016). rTMS was found to provide approximately 30–40% remission rate for TRD in various studies (Koutsomitros *et al.* 2021). Animal model studies that investigate the impact of magnetic field on neurons have shown that it can increase levels of BDNF (Janicak *et al.* 2008), influence motor learning and stimulate neural repair and axon outgrowth (Sherrard *et al.* 2018; Dufor *et al.* 2019) by the action of cryptochrome which is a magnetic sensor required in reinnervation. Meta-analysis done by Hao Li *et al.* exhibited a positive effect of rTMS on 48 adult patients with TRD (Li *et al.* 2021). rTMS was found to have an antidepressant effect also on adolescent patients. In a systematic review performed by Hett *et al.*, 14 studies were identified and all of them reported a reduction in depression scores in patients aged 14–25 (Hett *et al.* 2020).

Theta Burst Stimulation (TBS) is an alternative method based on the TMS protocol. TBS has been proposed in 2005 and it involves lower intensity of impulses and decreased stimulation time. TBS, similarly to TMS, targets the DLPFC region of the brain. There are three types of TBS: Intermittent TBS (iTBS), Continuous TBS (cTBS) and Intermediate TBS (imTBS) (Huang *et al.* 2005). Different types vary in train number and the time interval, after which the pulse is repeated. All procedures involve 600 pulses (Huang *et al.* 2005). The major difference between TMS and TBS for patients is that the deep TMS uses a 20-minute protocol, while TBS lasts for only 3 minutes (Huang *et al.* 2005). Decreasing therapy time might be more beneficial in terms of finances and time-management for patients. Amongst TBS methods, iTBS shows most promising results in decreasing depressive symptoms and suicidal thoughts in TRD (Mehta *et al.* 2022; Ekman *et al.* 2023). TBS was shown to provide higher response and remission rates compared to rTMS. A randomized controlled trial on 60 patients with depression performed by S. Bulteau *et al.* over the course of 6 months follow-up period exhibited 36.7% and 33.3% response rates, and 18.5% and 14.8% in the iTBS and 10 Hz rTMS groups respectively. However, a different study done by Spitz *et al.* has shown similar outcomes for both response and remission rates for iTBS and 10 HZ rTMS protocols (Spitz *et al.* 2022). Such findings suggest that more trials have to be performed in order to determine which method provides better response and remission rates. However, due to decreased treatment time, iTBS might be more appealing to patients. Despite promising results for TBS, this method carries a higher risk of epileptic seizures than TMS as it provides high-frequency pulse stimulation (Zhang *et al.* 2023). Other adverse effects include headaches and discomfort at the treatment site (Cristancho *et al.* 2020; Zhao *et al.* 2023). Overall, TBS protocols are safe and efficient for decreasing depressive symptoms. They are promising in terms of reducing patients' hospital exposure and lowering treatment costs. More studies are required to determine the best TBS method and to evaluate its superiority over TMS treatments.

Despite TMS being considered as safe, some adverse effects might occur. One of the most often side effects reported is transient headache which can be alleviated by simple analgesics (Janicak *et al.* 2008). Another discomfort reported after TMS sessions is the scalp pain and dizziness (Janicak *et al.* 2008; Hett *et al.* 2021). Some patients suffered from serious

adverse effects such as seizures. However, the majority of seizures were reported before the implementation of safety protocols. It is important to accurately identify seizure as it might be mistaken with myoclonic jerks. Patients that are at higher risk of TMS-related seizure are the ones suffering from neurological disorders that damage the brain structure, e.g., stroke, Alzheimer's, multiple sclerosis. Current guidelines recommend documentation of intake of drugs that can lower the seizure threshold. Other factors that lower the seizure threshold, e.g., alcohol consumption or sleep deprivation should also be considered. As stated in the US FDA's online database, only five seizure incidents were reported from 2009 to 2015. The data shows that although seizures occur, their numbers are small, even in populations at risk. Current data available, reduces the ability to accurately quantify seizure episodes, thus seizures are considered as rare (Rossi *et al.* 2021).

Deep brain stimulation

Another method of treating depression provided with biological background is deep brain stimulation (DBS) also used in treatment of diseases such as Parkinson disease, essential tremor and dystonia. Research continues to implement DBS into treatment of Alzheimer disease (Krauss *et al.* 2021).

Deep brain stimulation is an alternative for drug-resistant patients who do not respond to less invasive treatments. This neuromodulation technique supported by functional brain research and neuroimaging has both high efficiency and some possible associated risks. The mechanism of deep brain stimulation is based on a stimulator implanted in the chest skin and an electrode with its end placed in the specific brain areas. The stimulator sends impulses through the electrode and thereby disables or modifies the function of hyperactive in given disease brain areas and aligns the metabolism in relevant brain regions (Krauss *et al.* 2021). Results interpretation is possible thanks to neuroimaging (Antosik-Wójcińska *et al.* 2015).

Deep brain stimulation disables hyperactive brain areas in patients suffering from depression and increases activity in low active regions. The neurostimulation of any subcortical brain area may influence structures responsible for emotions (Krauss *et al.* 2021). The efficiency of DBS depends on targeted neuroanatomical locations most important of which are: subcallosal cingulate gyrus (SCG), nucleus accumbens (NAc), ventral capsule/ventral striatum or anterior limb of internal capsule (ALIC), medial forebrain bundle (MFB), lateral habenula (LHb) and inferior thalamic peduncle (Cattarinussi *et al.* 2022). Newest studies show that modifying white matter tracts may be more efficient for antidepressant response to DBS than targeting gray matter areas (Dandekar *et al.* 2018).

Drug-resistant patients treated with DBS have reported sudden serenity whereas the research showed decreased blood flow in the Brodmann area 25 which activity is directly connected to the duration of depressive episodes. (Krauss *et al.* 2021; Figee *et al.* 2022). The abnormal metabolic activity of the subcallosal cingulate gyrus (SCG), including Brodmann area 25, is an important part of mechanisms of treatment-resistant depression and therefore SCG remains the most targeted region in DBS for treatment-resistant depression (Mayberg *et al.* 2005). Another study showed that DBS of habenula reduces depressive episodes and exhibits efficacy in working with the brain's antireward system (Hamani *et al.* 2010). Recent studies name Brodmann area 10 and amygdala as another targets crucial for efficacy of treatment with DBS (Zhang *et al.* 2022).

DBS also attenuates neuroinflammation as well as inhibits pro-inflammatory factors that may cause mood improvement (Zhu *et al.* 2021).

Studies showed that approximately 60% of refractory patients treated with DBS across different targets responded well to the treatment. However, the results vary significantly between different patients. (Guo *et al.* 2023). Study investigating the influence of DBS of

the nucleus accumbens on drug-resistant depressive patients. showed that almost 50% of examined patients responded well to the treatment and had their mental health stabilized for the time of four years (Krauss *et al.* 2021). The constant improvement of mental state throughout the years shows the effectiveness of DBS (Figee *et al.* 2022).

Despite the proven effectiveness (Figee *et al.* 2021) of DBS including improvement of mood, activity and ability to feel pleasure, there is a risk of inducing some negative psychotic symptoms. Even though the number of positive responding patients prevails, there are some described cases of maniac or even, conversely to its objective, depressive episode after using DBS. Depressive symptoms include suicidal thoughts or attempts and hence need to long-term monitor the patients subjected to DBS. Furthermore there is risk of neurosurgical complications such as infections or intracerebral hemorrhage (Krauss *et al.* 2021). The potential risks of using DBS need to be factored during selecting the treatment method for depressive patients.

Further studies need to be conducted in order to completely understand mechanisms of deep brain stimulation and its potential long-term health consequences as well as its safety and overall efficacy.

2. Potential Non-pharmacological Treatment Methods

Acupuncture

Acupuncture is a method of transcutaneous nerve stimulation used to treat many conditions. It is one of many prospective therapies for reducing the symptoms of depression. It is considered a type of effective and safe medical practice. Advantages of this method include low cost and negligible side effects. Acupuncture in combination with drug treatment has been proven to produce better therapeutic effects (Bergfeld *et al.* 2022) than the drug alone. It minimizes the side effects of antidepressants which include nausea, insomnia, weight gain and sexual dysfunction (Bergfeld *et al.* 2022). Although the mechanism and efficacy (Bergfeld *et al.* 2022) of acupuncture are not known with certainty, it is claimed to modulate neuroplasticity, improve synapse function and affect microglia (Yang *et al.* 2022). Acupuncture is among the non-pharmacological treatments for depression. There is a distinction between isolated therapy and complementary therapy, which can be done in two styles: manual acupuncture and electroacupuncture (Bergfeld *et al.* 2022; Wang *et al.* 2022). More commonly used in medical practice is the manual method, which involves the percutaneous insertion of a thin metal needle into an acupoint (Yang *et al.* 2022) followed by manipulation, needle heating and massage. Electroacupuncture (Wang *et al.* 2022) is based on electrical stimulation instead of manual manipulation and thus can generate more consistent and reproducible results (Bergfeld *et al.* 2022). Depression, as the world's most severe mental disorder (Bergfeld *et al.* 2022), is one of the heterogeneous disorders that have arisen due to multiple pathomechanisms. Abnormalities lie in inflammation and neuroplasticity, among others (Bergfeld *et al.* 2022). The cause of depression is unknown, but the brain is important in its pathogenesis. It is claimed that changes in brain structure, chemical imbalances (Ulloa 2021; Bergfeld *et al.* 2022) and physiological abnormalities are directly responsible for the symptoms of depression. Structural and functional abnormalities have been demonstrated in specific brain regions and connections that affect cognitive and emotional phenomena (Bergfeld *et al.* 2022) occurring in the hippocampus, medial prefrontal cortex, anterior cingulate cortex, amygdala and semilocular nucleus. This is initiated at the level of cellular aberrations, resulting in the reduction of the above-mentioned brain areas. Acupuncture can work by regulating biochemical pathways and also restoring neuronal structures in patients suffering from depression. The monoamine neurotransmitter serotonin [5-HT] is also suspected to be involved in pathomechanism. Serotonin is formed by the metabolism of the exogenous amino acid tryptophan. Exogenous, which

is supplied to the body with the diet. In the pathomechanism of depression, serotonin undergoes excessive feedback resorption at the nerve synapse (Ulloa 2021; Bergfeld *et al.* 2022). In addition, there is increased autoreceptor activity, which inhibits the release of serotonin into the synapse (Ulloa 2021). Using acupuncture, the postsynaptic receptor for serotonin can be upregulated, restoring synaptic plasticity while reducing symptoms of depression. It has been observed that antidepressant drug therapy significantly reduces serotonin levels. This is one of the ways in which acupuncture supports antidepressant drugs, by increasing levels of 'FUNCTIONAL SEROTONIN' (Moncrieff *et al.* 2023). However, the theory of serotonin's involvement in the pathomechanism of depression is disputed. Most studies do not conclude that reduced or absent serotonin activity is observed in depressed individuals (Ulloa 2021) relative to healthy individuals. Nonetheless, many researchers support the supposition that serotonin deficiency results in depressive symptoms for a number of reasons. In the central nervous system, the most important component of the immune system is microglia, which is activated by pathogens and also by damaged synapses and neurons. Microglia has two types proinflammatory M1 and anti-inflammatory M2 (Wang *et al.* 2022). It has been shown that microglia, in addition to protecting brain tissue, activated proinflammatory types as an important part of the pathophysiology of depression. The interaction between inflammation and the brain's immune system can induce an imbalance of serotonergic and noradrenergic neurotransmission. The action of microglia is largely based on the secretion of pro-inflammatory (Yang *et al.* 2022) cytokines. The neurodegeneration and DEPRESSIONAL DISORDERS induced by these molecules act in two ways. The first is by reducing the activity of the enzyme indoleamine 2,3-dioxygenase. As a result, what decreases is the level of serotonin. The second involves an imbalance of serotonergic and noradrenergic neurotransmission through the hypothalamic-pituitary-adrenal axis. The use of acupuncture has contributed to a reduction in plasma levels of pro-inflammatory cytokines and thus a reduction in symptoms of depression. For mild and moderate forms of depression, isolated acupuncture therapy is used. Data collected over the years show that acupuncture has such good effects that additional therapeutic methods (Bergfeld *et al.* 2022; Yang *et al.* 2022) are not necessary. This was proven during a multicenter, randomized, controlled clinical trial. The subjects included peri-menopausal women with associated, moderate depressive symptoms. One part received drug treatment, the other part acupuncture. There were no differences among the subjects. In both pharmacologically and non-pharmacologically treated patients, improvements in quality of life and relief of depressive symptoms were observed (Bergfeld *et al.* 2022). Because of this, acupuncture is a potentially effective treatment for mild and moderate depression. Severe forms of depression (Bergfeld *et al.* 2022) require pharmacological treatment. More than half of patients respond well to treatment while a significant proportion do not. In addition, 63% of those taking medication have experienced side effects (Bergfeld *et al.* 2022). More than half of patients respond well to treatment while a significant proportion do not. In addition, 63% of those taking medication experienced side effects (Bergfeld *et al.* 2022). A large proportion of patients were forced to discontinue treatment by adverse effects resulting in relapse. Combining drug treatment with acupuncture has been shown to have a positive effect. It may reduce side effects, although due to the small number of studies it remains questionable. A meta-analysis and systematic review involving 1.046 people in a randomized controlled clinical trial confirmed that acupuncture combined with a selective serotonin reuptake inhibitor has an early onset of action, is better tolerated and initiates a strong antidepressant effect.

Physical activity

Physical activity is believed to reduce the symptoms of depression and also show (Davidson *et al.* 2022, Correia *et al.* 2022) a preventive effect in the development of depressive disorders. Physical activity refers to any type of body movement induced by muscular work and resulting in energy expenditure (Correia *et al.* 2022). Although the relationship between activity and depression is not fully elucidated, exercise affects a number of biological and psychosocial processes that are related to (Saran *et al.* 2021) the pathophysiology of depression. The benefits of physical activity for depression outweigh the risk reduction (Saran *et al.* 2021). In addition, exercise affects the endocrine system, self-esteem, social support, and neuroplasticity in oxidative stress or inflammation. Most importantly, it induces a wide range of biological changes in the brain, in addition to its impact on psychiatric disorders, physical activity also affects comorbidities that have contributed to or exacerbate the development of depression. An example is that exercise can reduce the risk of cardiovascular disease, (Saran *et al.* 2021; Correia *et al.* 2022) which is elevated in people with depression. It has been discovered that a cycle of biochemical transformations occurring under the influence of skeletal muscle activity prevents the adverse effects of stress by increasing production from brain nerve growth factor. This factor stimulates cell differentiation, promotes neuronal function by stimulating repair processes and also enhances memory pathways, thus having a beneficial effect on affective and cognitive functioning and the patient's daily activities. An example is people who do not engage in physical activity, where mental disorders are more likely to occur. It is possible to quantify the population burden of depression (Davidson *et al.* 2022) that is associated with too little physical activity and the potential impact of activity interventions on public health. Therefore, Mendelian randomization studies using the whole genome were conducted to support potential causal inference. Mendelian randomization is a surrogate method of potential causal inference that addresses genetic variation as a natural experiment in which individuals are generally assigned to higher and lower average levels of non-genetic exposure over their lifetime. Higher levels of physical activity were associated with a reduced likelihood of major depression. Genome-wide association study summary data were available for a combined sample of 611.583 adult participants. Mendelian randomization evidence suggests a preventive association between accelerometer-based activity and major depressive disorder (Kandola *et al.* 2019). Using genetic instruments identified from large-scale whole-genome association, solid evidence supports a protective relationship between physical activity (Kandola *et al.* 2019). and the risk of depressive disorder manifestation. Although sports have a positive effect on depression, (Davidson *et al.* 2022) some studies reveal that depression can cause a decrease in physical activity. This is mainly true for the severe form of the disease, where movement causes great suffering. Patients may not be able to cope with (Choi *et al.* 2019) the simplest activities. It has also been suggested that physical activity may in some way contribute to the development (Kandola *et al.* 2019; Davidson *et al.* 2022) of depression. Exercise that is characterized by excessive frequency and intensity, that is, exercise that exceeds the needs and capabilities of the body, may be associated with an increase (Choi *et al.* 2019) in oxidative stress. This stress is of great importance in the pathomechanism of depression. The type of activity is also important. Of the various physical activities, aerobic exercise is the most effective, and the most widely used. The effect of aerobic activities on modifying the volume of the hippocampus, which is reduced (Correia *et al.* 2022) in depressed patients, has been confirmed. In addition, environmental conditions are of paramount importance, as noise or neighborhood deprivation can reduce the mental health benefits of

activity. A recent meta-analysis of 49 prospective cohort studies comprising 1.837.794 averaged by the number of people exposed during the follow-up period and the duration of follow-up found that people with high physical activity were 17% less likely to be depressed than those with low physical activity (Zhang *et al.* 2019). Meta-analyses conducted collectively on a sample of 1.282 seniors with symptoms of depressive disorders show that the exercise used reduced the severity of the disorder and also improved the subjects' physical fitness. Although few empirical studies show evidence of ineffectiveness or confirm the low importance of physical activity in reducing symptoms of depression. This research focused on analyzing the correlation between physical activity and mental health attests that higher physical activity is associated with a lower risk of depression-specific symptoms, especially in adolescents (Wienicke *et al.* 2023). 1 in 9 cases of depression could be avoided if everyone in the population was physically active (Saran *et al.* 2021) at the level of current recommendations. Therefore, therapists and physicians should encourage their clients to exercise of all kinds to fill in the gaps in engaging in poor activities that lead to depression.

Probiotics

Recent studies have investigated the influence of intestinal microflora on mental state. Clinical studies on animals showed that probiotics containing particular bacteria strain influence brain operation and the results of behavioral tests proving thereby the connection between microbial gut bacteria and the central nervous system. This two-way communication called 'gut-brain axis' explains why supplementation of probiotics may be considered as a potential alternative therapy in treatment of depression (Sudak 2012).

The microbiota varies depending on the patient's health state. For instance, children diagnosed with autism had an increased number of Clostridium bacteria in comparison with healthy children (Herman 2019).

Irritable bowel syndrome suggests a connection between mental illnesses and inadequate bowel function since patients with IBS have increased depression morbidity rate (Finegold *et al.* 2022).

There are many examples in literature showing (Fond *et al.* 2014) differences in gut flora of depressive patients compared to the healthy controls. Tests on animals showed that intestinal bacterial colonization is crucial for proper development of both enteric and the central nervous system (Alli *et al.* 2022). The microbiota and probiotics both increase the intestinal wall's integrity and thus have a positive anti-inflammatory effect. There is a significant connection between inflammation and depression hence probiotics are a promising treatment method for treatment-resistant depression. Another way of influencing mental health by probiotics, except for regulation of inflammatory markers, is regulation of serotonin pathways (Minayo *et al.* 2021). Clinical trials during studies consisted of administering the following commensal bacterial stains: Lactobacilli (L.), Bifidobacteria (B.), Streptococcus (S.), or Lactococcus. Half of studies evaluating effects of daily probiotic intake on depression (Alli *et al.* 2022) reported improvement in terms of depressive episodes whereas the other half reported no change regarding depressive symptoms. However, some of the bacteria such as L. Plantarum P8 or L. Plantarum DR7 from the studies that concluded no change had positive effect on other symptoms for example reduced stress and anxiety, reduced cortisol level or reduced proinflammatory cytokines level. Depressed patients who were administered probiotics containing L. casei, L. acidophilus, and B. bifidum experienced general mood improvement (Alli *et al.* 2022). Another study investigating the influence of consuming yogurt containing different types of Lactobacilli and Bifidobacteria by healthy petrochemical workers revealed significant mental health improvement.

Probiotic administration was however not always successful and many studies showed

no difference in general mood of patients treated with probiotics (Sudak 2012; Alli *et al.* 2022).

Further studies need to be conducted in order to completely explore the details of gut-brain axis and possible long-term influence of using probiotic strains on mental health. The major differences in outcomes of various studies as well as too small groups of treated patients and other limitations such as patients' diet or assessment of the dose (Sudak 2012) preclude drawing a definitive conclusion regarding the effectiveness of probiotics in treatment of depression. However, (Minayo *et al.* 2021) probiotics, especially those containing Lactobacillus seem to have an effect on depression.

Yoga and mindfulness

Recently yoga and mindfulness have gained importance in terms of non-pharmacological depression treatment.

Mindfulness-based interventions that is MBIs (Liu *et al.* 2019) is an alternative therapy which is administered in order to improve the quality of life of patients with depression especially in terms of social and cognitive aspects. Mindfulness-based stress reduction (MBSR) program is based on focusing on the present bodily situation and noticing both internal and external experiences and connection between them, for example correlation between mental state and perceived physical pain (Chayadi *et al.* 2022). This intentional awareness has thereby a positive influence on both physical and mental conditions. Slightly changed version of MBSR which is MBCT (mindfulness-based cognitive therapy) was incorporated into treatment of depression and showed a high success rate (Chayadi *et al.* 2022). MBIs show how to accept emotional struggles and manage current mental state based on the interrelationship between the body and the mind (Chayadi *et al.* 2022). In a study conducted on oncology patients MBIs reduced symptoms of depression and anxiety. However, due to the individual patients' differences, low amount of studies and no proven long term effectiveness the results need to be further proven (Liu *et al.* 2019). Studies show that MBIs used with children and adolescents (Wilkos *et al.* 2013) as well as university students (Dunning *et al.* 2019) can also improve their mental health and reduce symptoms of depression.

Yoga is also a method used for mental health protection including treatment of depression. Historical articles prove the effectiveness of yoga exercises on psychiatric disorders (Gallo *et al.* 2023). Yoga helps to activate the parasympathetic nervous system and thereby induces relaxation (Gallo *et al.* 2023) and calmness (Żok *et al.* 2022). Yoga is also due to its low exercise intensity a suitable activity for pregnant women with depression who are often excluded from other treatment methods including antidepressants. Practicing prenatal yoga had an alleviating influence on mental health of pregnant women with depression, however had no effect on depression scores for those without depression (Gong *et al.* 2015). Another study showed the efficiency of mind-body exercise such as yoga on Chronic Obstructive Pulmonary Disease patients in terms of depression (Lin *et al.* 2022).

These techniques show how to accept emotional struggles and manage current mental state (Chayadi *et al.* 2022) based on the interrelationship between the body and the mind. These alternative methods seem to be efficient in terms of treating depression, however further studies need to be conducted in order to completely confirm their effectiveness. Since no negative effects were noticed, yoga (Żok *et al.* 2022) and mindfulness can be used as a supporting therapy.

Psychodelics

Due to a review, 'Prevalence and clinical course of depression' by Derek Richards (Li *et al.* 2019) one in three of people who are suffering from a major depressive disorder (MDD) will experience more than one depressive episode in their lifetime. Also a half of patients with depressive disorder do not respect policy of

antidepressants intake as soon as 6 months after initiation of treatment (Richards 2011). Relatedly, new treatments for depression are needed. Especially for those who do not respond to available antidepressants.

Psychedelic substances are a group of psychoactive substances that are associated with altered state of consciousness and perception (Solmi *et al.* 2022). There are two main categories of psychedelics; classic serotoninergic and atypical. Classic serotonergic psychodelics act on 5-HT2A receptors and we can distinguish psilocybin, N,N-dimethyltryptamine (DMT), ayahuasca, lysergic acid diethylamide (LSD). 3.4-methylenedioxymethamphetamine (MDMA) is an atypical psychodelic, that act on various receptors.

It is observed that more people are interested in psychedelics as therapy for depression in recent years. Lysergic acid diethylamide (LSD) and psilocybin were one of firsts which were used for treating drug resistant depression. This modulating property on the serotonergic neurotransmission system allows use psychodelics also in the treatment of major depressive disorder (MDD).

Psilocybin exerts its effects through agonism of the serotonin 5-HT2A receptors (González-Maeso *et al.* 2007; Halberstadt and Geyer 2011; Nichols 2016). The 5-HT2A receptors are necessary for the psychedelic experience, as the subjective effects of psilocybin seem to be blocked by 5-HT2A antagonists (Madsen *et al.* 2019). Psilocybin also has affinity albeit to a smaller extent, for several other serotonin receptors such as 5-HT1A and 5-HT2C (Vollenweider *et al.* 1998; Erkizia-Santamaria *et al.* 2022).

The serotonergic system plays a crucial role in regulating complex emotional behaviors (Rickli *et al.* 2016). For example, post-mortem analyses of depressed and suicidal individuals show increased expression of cortical 5-HT2A receptors (Pandey *et al.* 2002; Cools *et al.* 2018), while long-term antidepressant use is associated with decreased 5-HT2A receptor density (Shelton *et al.* 2009). Serotonin is involved in the feedback inhibition of the amygdala through the medial prefrontal cortex. (Gòmez-Gil *et al.* 2004) Amygdala hyperactivity is associated with depressive symptoms, and its normalization has been observed with antidepressant treatment (Fisher *et al.* 2009). As serotonergic agonists, psychedelics enhance the inhibition of the amygdala, and the resulting decrease in amygdala reactivity is linked to improved mood (Carhart-Harris *et al.* 2012; Sladky *et al.* 2015; Kraehenmann *et al.* 2016).

Ayahuasca

Ayahuasca is a traditional Amazonian brew which is made from the Banisteriopsis caapi vine and the Psychotria viridis leaf. The psychoactive effects are connected with specific alkaloids. Banisteriopsis caapi contains β-carboline alkaloids such as harmine, tetrahydroharmine, and harmaline, which are inhibitors of monoamine oxidase-A (MAO-A). MAO-A is an enzyme that normally degrades DMT in the digestive system.

This inhibition allows DMT to be orally active. Thereby it exerts its psychoactive effects during digestion as part of ayahuasca. Psychotria viridis contains N,N-Dimethyltryptamine (DMT), which has a powerful psychoactive compound. DMT is known as a classic serotonergic psychedelic, primarily acting as an agonist at the 5-HT1A and 5-HT2A receptors.

Additionally, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is another related short-acting serotonergic psychedelic. It is more like DMT, because of primarily acting as an agonist at the 5-HT1A and 5-HT2A receptors. In contrast, it has a lower binding affinity for dopamine receptors and norepinephrine transporters.

The interactions with the 5-HT receptors are central to the psychoactive and hallucinogenic effects of these compounds, contributing to the unconscious states during ayahuasca use (Carhart-Harris *et al.* 2012).

An open-label (Kalfas *et al.* 2023) revealed that Ayahuasca impacts on a reduction up

to 82% in depressive scores between baseline and 1, 7 and 21 days after drug intake. It was according to the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Anxious-Depression subscale of the Brief Psychiatric Rating Scale (BPRS).

The most significant impact was observed on depressed mood, feelings of guilt and suicidal ideation, which are typical depressive symptoms. (Osório *et al.* 2015).

Compared to placebo, ayahuasca also increased BDNF levels in people with treatment resistant depression and healthy controls (Harvey 2003). This investigation was correlated with reduction in MADRS scores ($rho = -0.55$, $p < .05$). It has also been suggested that serotonergic psychedelics may possess a unique ability to promote plasticity compared to other serotonergic agents. (Carhart-Harris *et al.* 2012; Muttoni *et al.* 2019).

Psilocybin

Psilocybin is a naturally occurring plant alkaloid which can be found in mushroom species, also known as 'magic mushroom,' It is also considered a prodrug of psilocin. Psilocybin influences on agonism of the serotonin 5-HT2A receptors. (González-Maeso *et al.* 2007; Halberstadt and Geyer 2011; Nichols 2016). The 5-HT2A receptors are necessary for the psychedelic experience, because that subjective effects of psilocybin are seem to be blocked by 5-HT2A antagonists (Carhart-Harris *et al.* 2012; Madsen *et al.* 2019).

Psilocybin influences on cognitive flexibility, cortical neural plasticity, and antidepressant responses in animals (Vaidya *et al.* 1997; Harvey 2003; Buchborn *et al* 2014; Vargas *et al* 2023).

The results of 'The experimental effects of psilocybin on symptoms of anxiety and depression': found that half of psilocybin antidepressant effect occurs at doses of 10.13 mg/70 kg, and 95% of the antidepressant effect occurs at doses of 41.14 mg/70 kg, achieving the optimal therapeutic effect. However, these results must be interpreted with caution, as with the exclusion of the only study including treatment-resistant patients (Hanks and Gonzales-Maeso 2013). Research showed that resistant patients mostly respond to higher doses of psilocybin (40 mg/kg).

Among the pool of patients with secondary depression, only 16% of patients presented MDD as a 'primary' diagnosis, other patients presenting adjustment and anxiety disorders.

These effects have also been observed in healthy volunteers, with psilocybin causing sustained improvements in wellbeing and optimism (Goodwin *et al.* 2022). This compound has a well established physiological and psychological safety profile, and has been rated one of the least harmful and possibly 'most beneficial' drugs of potential misuse by experts (Carhart-Harris and Nutt 2013; Griffiths *et al.* 2018).

Additionally animal studies have proved that psilocybin has a low addiction and physical dependence potential (Hasler *et al.* 2004). National surveys report showed low rates of abuse (European Monitoring Center for Drugs and Drug Addiction). In RCTs conditions, psilocybin appears to be well tolerated in the long term (Studerus *et al.* 2011; Griffiths *et al.* 2016; Johnson *et al.* 2018).

For patients who present a process of anxiety or psychotic symptoms, we can assume that higher doses of psilocybin may reduce therapeutic effectiveness by inducing dysphoric mood states, such as anxiety and fearful delusions. It can be primarily due to phenomena like ego-disintegration and loss of self-control (Griffiths *et al.* 2016; Perez *et al.* 2023). It is essential to note the paradoxical effect of serotonergic psychedelics, which can increase feelings of anxiety (Stoliker *et al.* 2022). The nature of psychedelic experiences is dependent on doses. Higher doses are associated with ego dissolution and potentially leading to a sense of loss of control, subsequent anxiety, or short-term psychosis-like symptoms (Carhart-Harris *et al.* 2014).

Neurobiologically, stimulation of 5-HT2A receptors has been linked to positive and negative aspects of the acute psychedelic state

including positive mood, anxiety, and psychotic symptoms. Carhart-Harris and colleagues propose the 'entropic brain' hypothesis by suggesting that increased cognitive entropy may explain paradoxical psychological effects (Griffiths *et al.* 2008; Hirschfeld and Schmidt 2021). These potential reactions prove that patients will achieve the ED95 for depressive symptom reduction at lower doses of psilocybin.

Additionally, Li and colleagues, in their meta-analysis, reported that the first or unique dose of psilocybin received was generally more impactful in decreasing depressive symptoms compared to subsequent doses (Rankaduwa and Owen 2023). Patients naive to hallucinogens might show a more significant response to psilocybin due to the novelty of the experience (Li *et al.* 2022). However, most studies provide narrow information on participants who use hallucinogens all their lifetime .

Therefore, the optimal dose of psilocybin for treating depression varies significantly among different patient subgroups. Caution should be exercised regarding dosage, especially for patients with psychiatric disorders other than depression (Studerus *et al.* 2011).

LSD

In contrast, lysergic acid diethylamide (LSD) is a semisynthetic psychedelic compound (Li *et al.* 2022). Reports from mid-twentieth century indicate that cancer patients who received LSD experienced profound psychospiritual insights. They led to long-standing improvements in mood and anxiety (Passie *et al.* 2008; Haijen *et al.* 2018). LSD is considered to be emotionally more intense than psilocybin. Also it has a higher cause of paranoia. Although high doses can result in severe anxiety or panic attacks. These adverse effects are generally prevented in a clinical setting with proper psychological support (Kast 1967).

LSD is primarily a 5-HT2A receptor partial agonist and a 5-HT1A receptor agonist but has also been shown to bind to 5-HT2C receptors (Egan *et al.* 1998; Osório *et al.* 2015; Das *et al.* 2016, De Gregorio *et al.* 2018).

LSD positively altered the processing of emotional information by decreasing the recognition of fearful and sad faces and enhancing emotional empathy and prosociality. We are aware of no other published data on the acute effects of LSD on emotion processing.

LSD (lysergic acid diethylamide) has been found to impair the recognition of negative emotions while enhancing emotional empathy, particularly in response to positive emotional situations.

Furthermore, LSD demonstrates prosocial effects, both subjectively and in behavioral assessments. These findings in healthy individuals suggest that LSD-assisted psychotherapy may be beneficial for patients, as it is expected to reduce the perception of negative emotions and strengthen the therapeutic alliance (Passie *et al.* 2008).

Summary of psychedelics

As we can observe, psychedelic administration causes statistically significant impact in reduction of depression and anxiety symptoms. These findings are consistent with prior investigations conducted on animals, healthy subjects, and anecdotal testimonials. (Kast *et al.* 1967; Richards *et al.* 1977; Riba *et al.* 2001; Hilber and Chapillon 2005; Farzin and Mansouri 2006; Santos *et al.* 2007; Griffiths *et al.* 2008; Fortunato *et al.* 2010). Visible improvement suggests a genuine therapeutic efficacy. What is more, the lack of significant reduction of depressing symptoms in control patients indicates that the antidepressant and anxiolytic effects can be attributed to psychedelic intervention. Participants also described the experience as spiritually meaningful, resulting in decreased feeling of hopelessness as well as improved a quality of life. Psychedelics' ability to provide acute symptom relief in one day is advantageous, especially when we compare it to current antidepressants, which take several weeks to work. This is because antidepressants delayed therapeutic effects can lead to non-compliance and contribute to increased morbidity

(Tylee *et al.* 2007; Machado-Vieira *et al.* 2010). Moreover, psychedelics' beneficial effects are maintained with impressive response rates for several months. This could mean that by comparison to the typical pharmacotherapy, administration is less frequent. In conjunction to the fact that exposure to treatment is monitored, it could help to overcome treatment resistance stemming from non-compliance (Kalfas *et al.* 2023).

Conclusions

While the current focus is on alternative non-pharmacological methods for treating depression, it is worth remembering the already established options. ECT, psychotherapy, VNS, TMS, and DBS have been implemented and recognized for decades. They are not only effective but also widespread. However, the rising percentage of depression cases has created a demand for new treatment methods. Alternative approaches for treating depressive disorders emerge annually. Possibilities range from solutions found in traditional Chinese medicine to unexpected branches of pharmacology, as shown in the 'psychedelics' section. The impact of lifestyle and mindfulness on cognitive processes and well-being is also significant. Some of the methods presented are widely accessible and affordable, making them available to patients and specialists. Non-pharmacological treatment methods have been shown to cause significantly fewer side effects compared to traditional approaches, such as antidepressant drugs. Moreover, they can be equally effective. However, more clinical trials are needed to prove the efficacy and safety of non-pharmacological methods for treating depression. Hopefully, with access to more advanced technology and an increasingly open-minded approach to the holistic nature of the human mind, scientists will discover groundbreaking solutions.

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REVIEW ARTICLE

HYBRID THERAPIES IN ORTHOPEDICS: A REVIEW OF THE POTENTIAL OF COMBINING BIOMATERIALS AND BIOLOGIC THERAPIES IN FRACTURE TREATMENT

TERAPIE HYBRYDOWE W ORTOPEDII: PRZEGLĄD MOŻLIWOŚCI POŁĄCZENIA BIOMATERIAŁÓW I TERAPII BIOLOGICZNYCH W LECZENIU ZŁAMAŃ

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ABSTRACT

This article presents the current state of knowledge on hybrid therapies in orthopedics, combining biomaterials with biological therapies as a novel approach to treating bone fractures. Traditional methods, such as immobilization and internal fracture stabilization, are confronted with modern strategies that enrich the biological environment of the fracture site to promote osteogenesis. The article discusses in detail the mechanical and biological properties of biomaterials, including metals, ceramics and biodegradable polymers, and their role in osteosynthesis. The critical importance of stem cells, particularly mesenchymal stem cells (MSCs), and growth factors (BMPs and TGF-β), which promote bone regeneration through osteoblast differentiation and modulation of inflammatory processes, is highlighted. Hybrid therapies, in which scaffolds (scaffolds) serve as carriers for stem cells and growth factors, have shown high efficacy in accelerating healing and providing structural stability. Despite their many benefits, such as reduced recovery time and higher quality of regenerated bone tissue, hybrid therapies face significant challenges, including the risk of immune reactions, complexity of manufacturing processes and high cost, which limits their widespread clinical application. The article points to the need for further research into manufacturing technologies and cost reduction, which could make advanced therapies more accessible and more widely used in orthopedics.

Keywords: biomaterials, growth factors, stem cells, bone regeneration, osteosynthesis, scaffolds, hybrid therapies

STRESZCZENIE

W artykule przedstawiono aktualny stan wiedzy na temat terapii hybrydowych w ortopedii, łączących biomateriały z terapiami biologicznymi jako nowatorskie podejście do leczenia

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złamań kostnych. Tradycyjne metody, takie jak unieruchomienie i wewnętrzne stabilizowanie złamań, skonfrontowano z nowoczesnymi strategiami, które wzbogacają środowisko biologiczne miejsca złamania, wspierając proces osteogenezy. W artykule szczegółowo omówiono właściwości mechaniczne i biologiczne biomateriałów, w tym metali, ceramiki oraz biodegradowalnych polimerów, i ich rolę w osteosyntezie. Podkreślono kluczowe znaczenie komórek macierzystych, szczególnie mezenchymalnych komórek macierzystych (MSC), oraz czynników wzrostu (BMP i TGF-β), które wspomagają regenerację kości poprzez różnicowanie osteoblastów i modulację procesów zapalnych. Terapie hybrydowe, w których scaffoldy (rusztowania) służą jako nośniki dla komórek macierzystych i czynników wzrostu, wykazują wysoką skuteczność w przyspieszaniu gojenia i zapewnieniu stabilności strukturalnej. Mimo wielu korzyści, takich jak skrócony czas rekonwalescencji i wyższa jakość regenerowanej tkanki kostnej, terapie hybrydowe napotykają na znaczące wyzwania, m.in. ryzyko reakcji immunologicznych, złożoność procesów produkcyjnych oraz wysokie koszty, co ogranicza ich szerokie zastosowanie kliniczne. Artykuł wskazuje na konieczność dalszych badań nad technologiami wytwarzania oraz redukcją kosztów, co mogłoby uczynić zaawansowane terapie bardziej dostępnymi i szerzej stosowanymi w ortopedii.

Słowa kluczowe: biomateriały, czynniki wzrostu, komórki macierzyste, osteosynteza, regeneracja kości, scaffoldy, terapie hybrydowe

Introduction

Effective fracture healing is a critical concern in orthopaedics, influencing patient outcomes and long-term limb functionality. The healing process involves complex biological and biomechanical mechanisms, such as intramembranous and endochondral ossification, essential for restoring bone integrity. Successful healing is characterized by timely bone union, achieving both anatomical alignment and functional recovery. However, fracture nonunion, defined as the failure to heal within an expected timeframe, affects 10–15% of surgically managed cases and presents significant clinical challenges. Traditional treatments, including cast immobilization and open reduction with internal fixation (ORIF), have been foundational for managing fractures, relying on mechanical stability to allow natural biological processes. Yet, advances in surgical techniques, especially minimally invasive approaches and regenerative therapies, have revolutionized fracture management by focusing on enhancing the biological environment at the fracture site through growth factors, stem cell therapy, and bioactive scaffolds, all of which can significantly improve healing rates.

To investigate these advancements, a comprehensive literature review was conducted in major databases, including PubMed, Scopus, and Web of Science, using keywords like "hybrid therapies in orthopedics," "biomaterials in fracture treatment," "biologic therapies in orthopedics," and "bone regeneration with biomaterials." The search was limited to publications from the last 15 years, ensuring the inclusion of the most current and pertinent data. Twenty-five highly relevant scientific articles were selected and thoroughly analyzed for their contributions to the development of hybrid theories in fracture healing. These theories propose that the interplay between mechanical stability and biological factors determines healing outcomes, advocating for a multifaceted approach tailored to individual patient characteristics, fracture type, and health status. This review contrasts traditional and modern therapeutic strategies, emphasizing the importance of a personalized approach in mitigating the risks of delayed union and nonunion while exploring the clinical potential of combining biomaterials with biological therapies in orthopaedics.

Types of biomaterials in osteosynthesis

Osteosynthesis, a procedure used for internal bone fixation, relies on biomaterials to provide mechanical support and facilitate bone healing. Biomaterials used in osteosynthesis can be broadly classified into three categories: metals, ceramics, and biodegradable polymers. Each material type has its unique mechanical and biological properties that dictate its applications and limitations in orthopedic surgery.

Metals

Titanium and stainless steel are among the most widely used metals for osteosynthesis due to their mechanical properties. Titanium alloys, in particular, offer high strength, biocompatibility, and corrosion resistance, making them a reliable choice for bone fixation in orthopedic. Titanium's biocompatibility allows for osseointegration, where the bone grows around the implant without rejection. However, titanium implants may require removal due to irritation or visibility under the skin after healing, especially in maxillofacial surgeries (Marin *et al.,* 2024; Filip *et al.,* 2022) Stainless steel is another commonly used metal, especially in trauma surgeries. While cheaper than titanium, it is more prone to corrosion and wear. This can sometimes result in adverse tissue reactions, which limits its long-term use (Augustine *et al.,* 2024).

Ceramics

Hydroxyapatite and tricalcium phosphate (TCP) are examples of ceramics used in osteosynthesis. These bioceramics are valued for their osteoconductive properties, meaning they support bone ingrowth. Hydroxyapatite, a naturally occurring component of bone, is often used to coat metal implants, enhancing the integration of the implant with the surrounding bone. TCP is biodegradable, and as it breaks down, it gets replaced by natural bone. Despite their biocompatibility, ceramics have limited mechanical strength, which makes them unsuitable for load-bearing applications (Augustine *et al.,* 2024).

Biodegradable polymers

Polylactide (PLA), polyglycolide (PGA), and their copolymers are increasingly being used as biodegradable materials in osteosynthesis. These materials degrade over time, eliminating the need for a secondary surgery to remove the implant, as is often required with metals. PLA is particularly useful in situations where temporary support is needed, and its degradation products are metabolized by the body into carbon dioxide and water. However, the mechanical strength of biodegradable polymers is generally lower than metals, and they may induce inflammatory responses (Marin *et al.,* 2024; Augustine *et al.,* 2024).

Mechanical and biological properties

Mechanical Properties: Metals such as titanium and stainless steel exhibit high tensile strength, making them suitable for load-bearing applications. Ceramics, while strong in compression, are brittle and can fracture under tensile stress. Biodegradable polymers, although advantageous due to their resorbable nature, lack the strength and stiffness required for major weight-bearing applications (Filip *et al.,* 2022). Biological Properties: Titanium alloys and hydroxyapatite-coated ceramics exhibit excellent biocompatibility, promoting osseointegration without causing significant inflammatory responses. Biodegradable polymers are designed to be absorbed by the body, reducing the risk of long-term complications associated with permanent implants. However, the degradation of some polymers can result in local inflammatory reactions, necessitating careful material selection (Marin *et al.,* 2024; Augustine *et al.,* 2024).

Role of stem cells in osteogenesis

Stem cells play a key role in the process of osteogenesis both during the development of the body and during regeneration after damage.The most important type in this process are mesenchymal stem cells (MSCs). Their source can be umbilical cord blood, adipose tissue, bone marrow and dental pulp. Induced pluripotent and genetically modified

stem cells are also used (Wang *et al.,* 2024). The differentiation of MSCs into osteoblasts is controlled by multiple signaling pathways, such as the Wnt/β-catenin pathway and bone morphogenetic proteins (BMPs). In particular, the Wnt/β-catenin pathway plays a key role in promoting osteoblast proliferation and matrix mineralization, leading to new bone formation (Wang *et al.,* 2024; Chen *et al.,* 2022). In research, MSCs are often used in combination with various biomaterials. Examples of such materials include collagen or hydroxyapatite scaffolds, which promote regeneration of bone defects and accelerate repair processes (Garrison *et al.,* 2010).

Growth factors (BMP, TGF-β) and their effects on fracture healing

Growth factors play a significant role in the phenomenon of fracture healing. One of the most important factors is bone morphogenetic protein (BMP), which initiates the process of osteogenesis by affecting the differentiation of mesenchymal stem cells into osteoblasts (Niu *et al.,* 2023) . Transforming growth factor beta (TGF-β) promotes osteoblast proliferation and differentiation. In addition, it promotes extracellular matrix deposition and mineralization. It has also been reported that TGF-β modulates inflammation and promotes angiogenesis, which further supports bone repair (Asparuhova *et al.,* 2018). TGF-β and BMP-2 have been shown to act in synergy to support osteoblast differentiation and bone matrix mineralization. Their joint application leads to improved proliferation and differentiation of osteoblast precursor cells, as well as increased mineralization (Balmayor *et al.,* 2015).

Gene therapies targeting bone tissue regeneration

The main approaches include in vivo and ex vivo therapies. For in vivo therapies, viral or non-viral vectors are directly inserted into the site of bone damage, where they transduce local cells to promote osteogenesis. One of the most commonly used vectors is adenovirus, which carries a cDNA containing the gene encoding BMP-2, Runx2 or VEGF. The most commonly used non-viral methods include cationic polymers and cationic liposomes. Hydrogels such as alginate, fibrin or hyaluronic acid are also used. Another innovative method is sonoporation, which uses ultrasound in combination with microbubbles (Medhat *et al.,* 2019).

Effect of immunomodulatory properties of mesenchymal stem cells on bone regeneration

Mesenchymal stem cells (MSCs) play an important role in bone regeneration due to their immunomodulatory properties. In the early stages of bone healing, MSCs can inhibit T-lymphocyte activity, preventing excessive inflammation that could delay regeneration. Their ability to secrete cytokines such as IL-10 and TGF-β promotes the transformation of the inflammatory response from pro-inflammatory to anti-inflammatory, which promotes osteoblast differentiation (Qi *et al.,* 2021).

Concept of hybrid therapies in orthopedics

Hybrid therapies in orthopedics, combining biomaterials with biological therapies, are emerging as a promising approach in fracture treatment. These approaches aim to improve bone regeneration by integrating mechanical and biological components, which promotes both structural stabilization and activation of healing processes. Biomaterials are used for structural support, while stem cells and growth factors promote bone regeneration. Studies indicate that the combination of scaffolds (scaffolds) with stem cells can significantly accelerate the healing process, and their synergistic action can lead to better clinical outcomes compared to traditional methods (Wu *et al.,* 2022).

Scaffolds (scaffolds) as carriers of cells and growth factors

Autogenous and allogenic grafts are used to repair damaged bones, which have some limitations. Another solution is the usage of exogenous scaffolds as bone substitutes

(Zeng *et al.*, 2018). We can divide scaffolds into biological and synthetic. The former can be beads, natural polymers and demineralized bone matrix, such as collagen sponge or gel foam. Examples of synthetic scaffolds include porous metals, synthetic polymers and calcium phosphates (CaPs). Tissue engineering scaffolds with growth factor are used to improve bone regeneration by inducing bone cells to adhere and proliferate (Zhang *et al.*, 2014). One study showed that porous silk scaffolds can serve as a vehicle for nucleated cells to regenerate bone (Zhu *et al.*, 2021).

Surface modifications of biomaterials for better osteointegration

Surface modifications of biomaterials are important for improving the osteointegration and antimicrobial properties of medical implants (Yu *et al.*, 2022). One publication studied the modification of Polyetheretherketone (PEEK) to improve osteointegration. Among the methods used were melt extrusion, laser ablation, sandblasting, sulfonation, plasma treatment and accelerated neutral atom beam. These techniques have been shown to effectively promote osteointegration while maintaining mechanical properties (Lackington *et al.*, 2020).

Efficacy and healing time

Studies have shown that hybrid therapies can significantly accelerate fracture healing compared to conventional methods. Traditional treatments focus on mechanical stabilisation, whereas hybrid therapies incorporate biological elements that actively promote bone regeneration, particularly through bone morphogenetic proteins (BMP-2 and BMP-7). Such therapies enhance the proliferation and differentiation of cells at the fracture site, allowing for faster healing compared to standard techniques (Kaspiris *et al.*, 2022; Marongiu *et al.*, 2020). Moreover, mesenchymal stem cells are increasingly being integrated into fracture treatment due to their ability to differentiate into osteoblasts and chondrocytes, further contributing to bone regeneration. Evidence suggests that hybrid therapies can reduce healing time by 30–50% compared to standard methods, particularly in the case of complex and challenging fractures (Marongiu *et al.*, 2020). The integration of biological therapies with biomaterials not only improves the speed of healing but also enhances the quality of bone repair, which is crucial for a faster return to physical function for patients (Kaspiris *et al.*, 2022; Marongiu *et al.*, 2020). Patients treated with modern hybrid therapies are less likely to require reoperation, experience lower levels of pain, and exhibit greater overall mobility in the long term (Kaspiris *et al.*, 2022).

Technical and production challenges

The technical challenges associated with hybrid therapies include difficulties in standardising the production of implants and biomaterials. Each material used in hybrid implants must be precisely manufactured, which is both time-consuming and costly. Processes such as 3D printing, employed for the customisation of scaffolds, still require refinement, particularly regarding biocompatibility and optimisation for integration with bone and surrounding tissues. Furthermore, the development and testing of novel biomaterials, as well as their combination with cell-based therapies, necessitate advanced analytical techniques, complicating their production and market introduction (Brown *et al.*, 2024; Xue *et al.*, 2022).

Immune responses and infection risk

One of the primary risks associated with hybrid therapies is immune reactions, which leads to inflammation, infection, or even implant rejection. The use of foreign materials, even those that are biocompatible, carries an inherent risk of infection, particularly when advanced techniques such as cell therapy or implants with antibacterial coatings are employed. Despite the use of antibacterial coatings, there is still a risk of infection with antibiotic-resistant bacteria (Riester *et al.*, 2021).

Costs and accessibility of advanced therapies

The cost of hybrid therapies represents one of the most significant barriers to their widespread use. High costs related to production, clinical research, and the personalisation of implants make these therapies inaccessible to the majority of patients. Additionally, the limited availability of advanced technologies such as 3D printing and cell therapies restricts their application in fracture treatment to specialised centres. The development of technology and reduction of production costs could improve the accessibility of these therapies, although this will require many years of further research and investment (Xue *et al.,* 2022; Riester *et al.,* 2021).

Summary and conclusions

The article explores advancements in fracture healing, comparing traditional and modern approaches in orthopaedics. Traditional treatments, such as cast immobilisation and internal fixation, focus on mechanical stability, but newer methods aim to improve the biological environment for regeneration. This includes using growth factors, stem cell therapy, and bioactive scaffolds, all enhancing healing rates and addressing complications like nonunion, affecting 10–15% of fractures managed surgically. Biomaterials are central to osteosynthesis, classified into metals, ceramics, and biodegradable polymers, each with unique properties and applications. Metals like titanium are favoured for their strength and biocompatibility but can require removal post-healing. Ceramics, such as hydroxyapatite, promote bone ingrowth but lack load-bearing strength. Biodegradable polymers eliminate the need for removal but may cause inflammatory responses as they degrade. Biological therapies support fracture healing through stem cells, growth factors, and gene therapies. Mesenchymal stem cells (MSCs) aid in osteoblast differentiation, while growth factors like BMP and TGF-β enhance bone regeneration. MSCs with its immunomodulatory effects also reduce inflammation that supports healing. Hybrid therapies, combining biomaterials with biological treatments, present an enhanced bone stability and accelerate regeneration, improving patient outcomes, reducing healing time, and lessening the likelihood of reoperation. However, hybrid therapies face challenges like immune response risks, production complexity, and high costs, limiting accessibility. Improved technologies, cost reduction, and further research are essential for widespread adoption of these advanced treatments.

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CASE REPORT

CASE REPORT: DIAGNOSIS AND MANAGEMENT OF CARPAL TUNNEL SYNDROME IN A PATIENT WITH OLIGODACTYLY

OPIS PRZYPADKU: DIAGNOSTYKA I POSTĘPOWANIE W ZESPOLE CIENI NADGARSTKA U PACJENTA Z OLIGODAKTYLIĄ

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ABSTRACT
Carpal tunnel syndrome (CTS) is a frequent neuropathic condition that can result in numbness, pain, and tingling sensations in the fingers and hand. It often affects individuals who have specific risk factors, such as injuries, pregnancy or certain medical disorders.

In this case report, we describe a patient presenting with symptoms of carpal tunnel syndrome (CTS), along with radial longitudinal deficiency, which represents a spectrum of upper limb dysplasias and hypoplasias. The patient exhibited unilateral thumb and radial artery hypoplasia, with the ulnar artery being the exclusive source of blood supply to the hand. Initially, the patient reported mild CTS symptoms that gradually worsened, impairing her daily activities. An ultrasound confirmed the diagnosis, and surgical release of the carpal tunnel was performed. Following surgery, the patient reported significant improvement in her symptoms, with her hand and finger strength and sensation returning to baseline.

The aim of this case report is to enhance the knowledge and skills of orthopedic practitioners by presenting a detailed account of the diagnosis and management of carpal tunnel syndrome in a patient with oligodactyly and an unique anatomical variation of hand vascularity. We discuss the topic of radial longitudinal deficiency and typical anatomical variations in human hand vascularity.

Keywords: Carpal tunnel syndrome, oligodactyly

STRESZCZENIE
Zespół cieśni nadgarstka (ZCN) jest częstym schorzeniem neuropatycznym, które może powodować drętwienie, ból i uczucie mrowienia w palcach i dłoni. Często dotyka osób z określonymi czynnikami ryzyka, takimi jak urazy, ciąża lub niektóre schorzenia.

W niniejszym opisie przypadku przedstawiamy pacjentkę z objawami zespołu cieśni nadgarstka (ZCN) oraz niedoborem promieniowym podłużnym, który reprezentuje spektrum dysplazji i hipoplazji kończyny górnej. U pacjentki stwierdzono jednostronną hipoplazję kciuka oraz tętnicy promieniowej, przy czym tętnica łokciowa była jedynym źródłem zaopatrzenia dłoni w krew. Początkowo pacjentka zgłaszała łagodne objawy ZCN, które stopniowo nasilały się, utrudniając jej codzienne czynności. Badanie ultrasonograficzne potwierdziło diagnozę, a pacjentka przeszła chirurgiczne uwolnienie cieśni nadgarstka. Po operacji zgłaszała znaczną poprawę objawów, z powrotem siły i czucia w dłoni i palcach do stanu wyjściowego.

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Celem tego opisu przypadku jest poszerzenie wiedzy i umiejętności ortopedów, poprzez szczegółowy opis diagnozy i leczenia zespołu cieśni nadgarstka u pacjentki z oligodaktylią i unikalnym wariantem anatomicznym unaczynienia ręki. Omawiamy również zagadnienie niedoboru promieniowego podłużnego oraz typowe warianty anatomiczne unaczynienia ręki.

Słowa kluczowe: zespół cieśni nadgarstka, oligodaktylia

Introduction

Carpal tunnel syndrome (CTS) encompasses a spectrum of clinical manifestations that result from median nerve entrapment within the carpal tunnel. Patients typically report experiencing pain and paresthesia, and less frequently, weakness, in the distribution of the median nerve. CTS is the most commonly observed compressive focal mononeuropathy in clinical practice, with an estimated prevalence of 1 to 5 percent in the general population. Notably, it is more prevalent in females (Pourmemari *et al.,* 2018 and Atroshi *et al.,* 1999). Multiple factors increase the risk of developing CTS, including diabetes mellitus (Albers Leach *et al.,* 1996 and Leach *et al.,* 1968), arthritis (Shiri 2016), thyroid disorders (van Dijk *et al.,* 2003), pregnancy (Padua *et al.,* 2001), and wrist trauma (Pope and Tang 2018) (Schnetzler 2008). The contribution of repetitive hand and wrist use and workplace factors to the onset of CTS is an area of ongoing debate among experts (Padua *et al.,* 2016; Shiri and Falah-Hassani, 2015; Mediouni *et al.,* 2014).

Radial longitudinal deficiency is a condition characterized by a spectrum of dysplasias and hypoplasias in the upper limb, primarily affecting the radial aspect of the forearm, wrist, and hand. It involves bony abnormalities in the thumb and radius, as well as deficiencies in muscles, nerves, vessels, and joints, leading to significant functional impairments in the upper extremity (Bhat and Acharya, 2020; Maschke *et al.,* 2007; Ekblom *et al.,* 2013). This condition may be associated with other medical conditions such as TAR (thrombocytopenia absent radius) syndrome, Fanconi's anemia, Holt-Oram syndrome, and the VATER (vertebral anomalies, anal atresia, tracheoesophageal fistula, esophageal atresia, renal agenesis) or VACTERL (vertebral anomalies, anal atresia, cardiac abnormalities, tracheoesophageal fistula, renal agenesis, and limb defects) association, which involve various concomitant anomalies in different organ systems (Maschke *et al.,* 2007; Ekblom *et al.,* 2013; Forman *et al.,* 2020).

In this article, we present a case of CTS in a patient with radial longitudinal deficiency. Although our literature search did not yield strong evidence that supports a correlation between congenital hand anomalies and the development of CTS, it is plausible that such a relationship exists.

Case presentation

A 36-year-old female with a history of left thumb hypoplasia presented to the clinic with complaints of pain, numbness, and tingling in her left hand and fingers. Her symptoms had started in April/May of 2022, and had gradually worsened over time, affecting her daily activities such as holding a cup, combing her hair, and using her phone. She also reported frequent episodes of hand numbness and tingling, as well as decreased hand grip strength, resulting in objects slipping out of her hand. Her pain was most severe in the summer of 2022, and was worse at night and on raising her arm. Her symptoms improved when she lowered her hand. She had been taking various pain medications, including ibuprofen, acetaminophen, dexamethasone, and ketoprofen, with ketoprofen being the only medication providing relief.

The patient had a history of oligodactyly and she had no other medical conditions and did not take any regular medications.

The patient did not present with any additional disorders often associated with radial longitudinal deficiency, including anemia and various organ anomalies. She denied any history of trauma or repetitive hand motions. During pregnancy, her mother was living in Poland when the Chernobyl disaster occurred, which might have contributed to the development of congenital abnormalities of the patient. The patient had sought medical attention in July/August of 2022, and underwent an electromyography (EMG), which was suggestive of mild nerve compression but not CTS. The diagnosis of CTS was made in November 2022 after an ultrasound of the hand and wrist showed evidence of median nerve compression at the wrist (Figure 1, 2). Furthermore, the ultrasound revealed the absence of the left radial artery in the patient, with the ulnar artery being the sole source of blood supply to her hand. Nevertheless, the patient was qualified for a decompression surgery of the compressed nerve.

the transverse ligament. The soft tissues were dissected until reaching the transverse carpal ligament. A grooved probe was then inserted under the ligament, covering the nerve and lifting the superficial tissues, and the ligament was cut posteriorly, partially subcutaneously, along with a part of the forearm fascia, approximately 1.5 cm proximally from the wrist flexure line. The thickened ligament was found to be constricting the nerve, which was also thickened proximally. Hemostasis was checked, and a Redon drain was placed. The wound was sutured, and a sterile dressing was applied.

The surgery was challenging due to the fact that the ulnar artery, which was the only artery supplying the patient's hand, was located near the median nerve.

The patient underwent surgical release of the carpal tunnel in January 2023. The surgery was uneventful, and the patient reported significant improvement in her symptoms post-surgery. She reported no significant

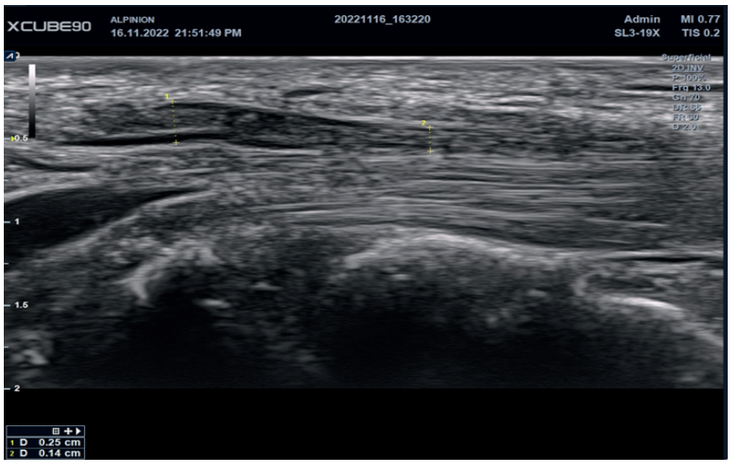

Figure 1. A longitudinal cross-section of the median nerve. The nerve is narrowed and appears more echogenic below the transverse ligament. There is an edema in the proximal portion of the nerve, which is characterized by thickening, reduced echogenicity, and disrupted fibrillar echostructure

Management and outcome

The procedure performed to this patient was a release of the left median nerve, done under Esmarch's tourniquet for ischemia control (6 minutes ischemia time for nerve release). The arcuate incision was performed above

pain after surgery, but did experience some pulsating sensations in her fingers. No immobilization was applied. Patient was discharged with instructions for hand therapy and to avoid repetitive hand motions for a few weeks. At the follow-up appointment, the patient

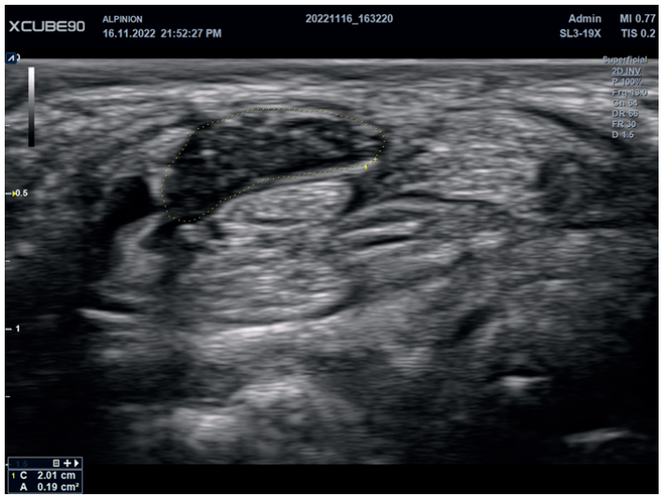

Figure 2. Transverse section through the median nerve proximal to the carpal tunnel. The cross-sectional area is enlarged, measuring 0.19 cm², which exceeds the normal range of less than 0.1 cm². The hypoechogenic ulnar artery is visible adjacent to the nerve

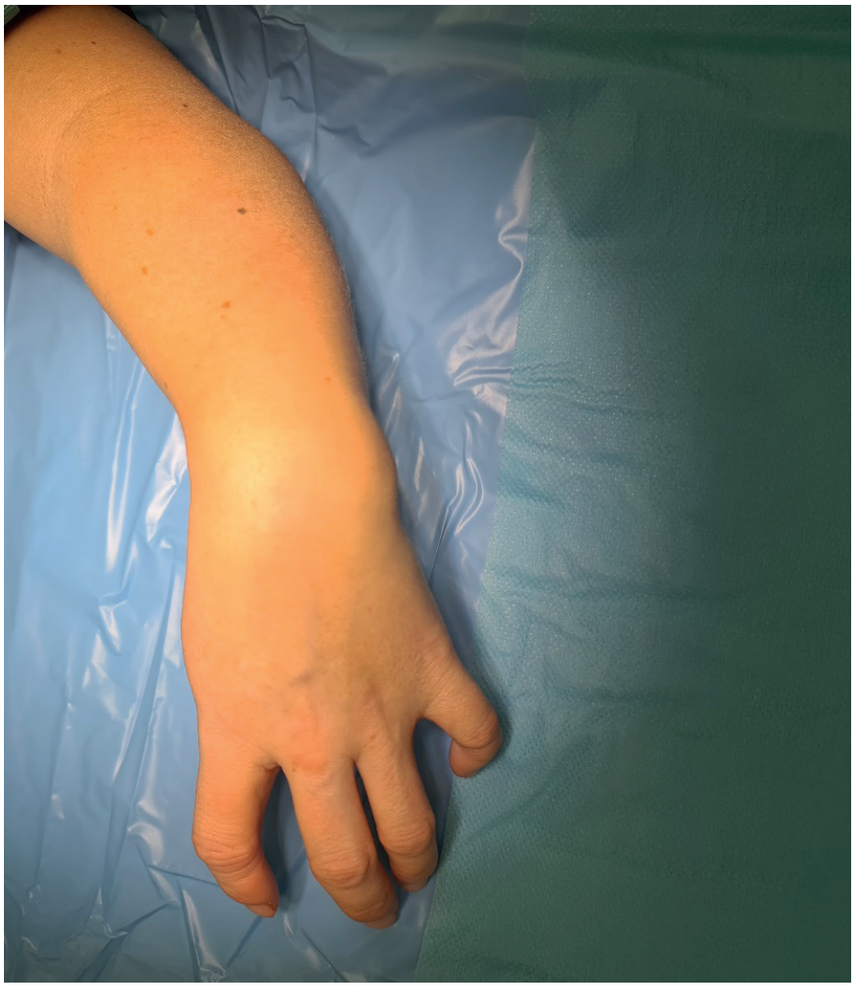

Figure 3. A patient's left hand prior to surgery

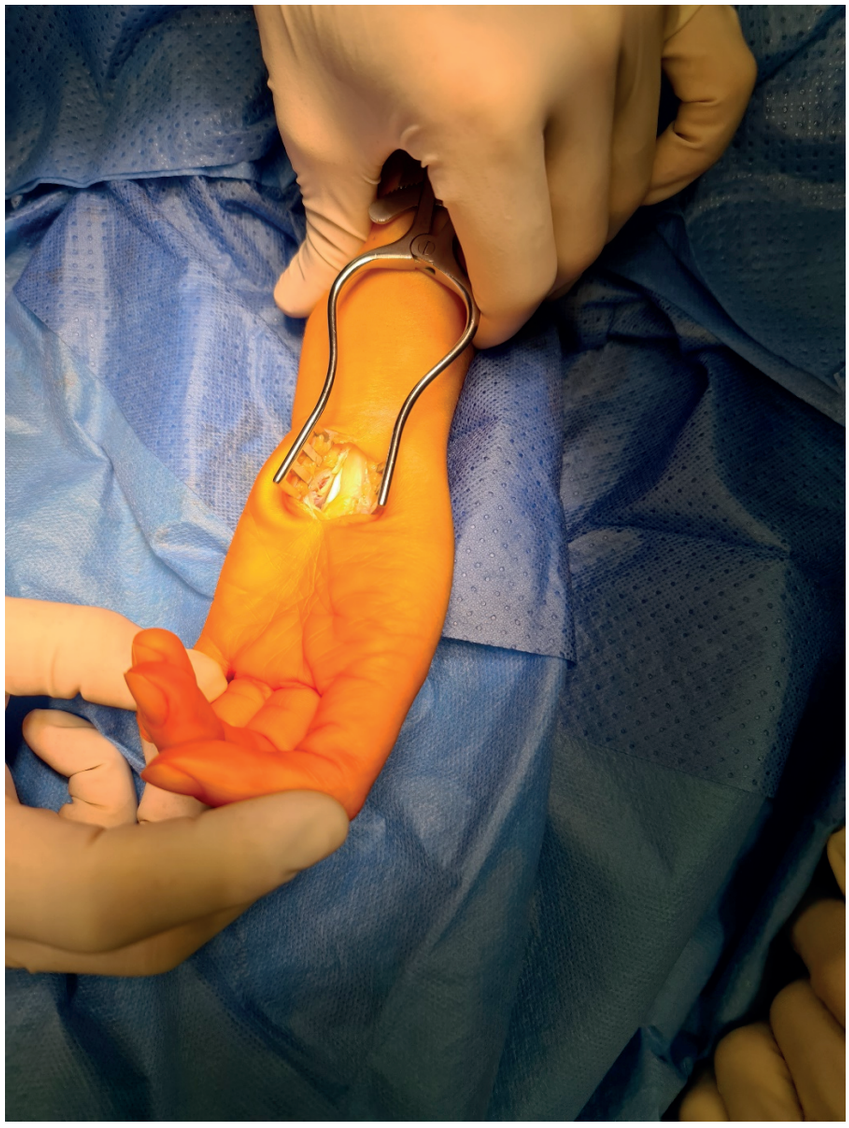

Figure 4. A narrowed nerve visualized after transecting the transverse ligament

reported full recovery of her hand strength and sensation. She had no complaints related to the surgery.

Discussion

The presented case report describes a patient with CTS, which is a common peripheral nerve entrapment disorder. The patient reported experiencing numbness, tingling, and weakness in her hand, which progressively worsened over several months, making daily activities such as holding objects and grooming difficult. The diagnosis of CTS was confirmed through ultrasound imaging, and the patient subsequently underwent surgical intervention to relieve the compression of the median nerve in the wrist.

Surgical intervention involving the transection of the transverse carpal ligament is considered the most effective treatment for releasing the nerve. The surgical decompression can be performed through different approaches, including the traditional open technique (involving a long longitudinal wrist incision and direct visualization of the ligament), minimally invasive approach (with a shorter wrist incision), or endoscopic technique (Padua *et al.*, 2016). In our practice,

we often opt for minimally invasive techniques, which have shown better outcomes compared to the standard open approach. These include fewer complications, higher patient satisfaction, improved symptoms, positive results on Tinel's, Phalen's, and compression tests, enhanced electrodiagnostic assessment, grasp strength evaluation, and faster recovery of the ability to perform personal tasks (Aslani *et al.*, 2012; Tarallo *et al.*, 2014; Elsharif *et al.*, 2014). However, in the case of the discussed patient, we decided to perform a longer incision to ensure better visualization of the ulnar artery. The use of Esmarch's tourniquet is a common technique for controlling ischemia during surgery. The insertion of the grooved probe under the ligament is a technique that can help protect the nerve during the procedure. The post-operative care of the patient will include monitoring for signs of nerve function recovery and wound healing. The use of a Redon drain and a sterile dressing is standard practice to prevent infection and promote healing.

It is worth noting the anatomical variations in arterial vascularization within the wrist when discussing this case. Anatomical variability of arterial vessels of the wrist is especially relevant in surgical procedures, such as wrist arthroscopy, which require a thorough understanding of the arterial anatomy of the region to avoid inadvertent injury to the vascular structures. The superficial palmar arch can be classified into three main types (Adachi and Hasebe 1928). The most common type is the ulnar type (typus ulnaris; 60%), which lacks a connection between the ulnar artery and the radial branch of the superficial palmar arch, which is then very weak. In the ulnar type, the area supplied by the ulnar artery may include, although rarely, all fingers. The next most numerous type is the radioulnar type (typus radioulnaris; 32%), in which both the ulnar artery and the radial branch of the superficial palmar arch supply the fingers. The least numerous type is the median-ulnar type (typus medianoulnaris; 8%), which occurs when the accompanying artery of the median nerve is well developed and replaces the branch of the radial artery; together with the ulnar artery, it then supplies the fingers. This type is also highly variable. The two vessels can join together to form a complete arterial arch, or they can branch directly to the fingers without connecting to each other. The median nerve's accompanying artery usually becomes the second finger's common digital artery. The radial half of the hand is mainly supplied by the deep palmar arch and dorsal metacarpal arteries, while the ulnar half mainly originates from the brachial artery. The position of the deep arch relative to the ulnar nerve branch is variable and if one palmar arch is diminished, the dorsal metacarpal arteries can compensate (Bochenek and Reicher 2012). The patient's case does not fit into any of the aforementioned three variants. The only artery observed in the patient at the wrist level was the ulnar artery. Furthermore, it was located very close to the median nerve, which posed a challenge during the surgery. Preoperative ultrasound examination of this finding enabled the surgeon to be prepared for this situation, avoiding any unfavorable surprises during the procedure.

The patient's positive treatment outcomes highlight the importance of early diagnosis and prompt treatment of CTS, as delaying treatment can result in further nerve damage and decreased quality of life. It also emphasizes the significance of considering a patient's medical history and potential risk factors in the diagnostic process.

There is currently no clear evidence to suggest that individuals with oligodactyly are at an increased risk of developing CTS. Nevertheless, certain sources appear to support the notion of a genetic predisposition to CTS (Hakim *et al.*, 2002). We have identified another case of carpal tunnel syndrome in an individual with thumb hypoplasia (Mace *et al.*, 2014). In this instance, the hypoplasia was part of Holt-Oram syndrome. The median nerve was significantly displaced towards the radial side, and a correlation

was suggested between this finding and the concurrent hypoplasia of the scaphoid bone. In a separate case (Robati *et al.,* 2009), a patient diagnosed with both carpal tunnel syndrome and Holt-Oram syndrome exhibited an unusual presence of the flexor digitorum superficialis muscle belly within the carpal tunnel, potentially contributing to the development of carpal tunnel syndrome.

Summary

Carpal tunnel syndrome is a common condition that can significantly affect a patient's daily life. Its diagnosis is typically straightforward, and treatment options range from conservative measures to surgical intervention. However, it is essential to consider a patient's medical history and perform examination and imaging to ensure correct diagnosis and appropriate treatment. In this case, the ultrasound examination in the patient with oligodactyly showed typical CTS image, but additionally we were able to find the absence of the radial artery which had an impact on the surgical procedure and increased our awareness during surgery.

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Książki:
Rang, H. P., Dale, M. M., Ritter, J. M., Moore, P. K. Pharmacology. 5th Ed. Edinburgh: **Churchill Livingstone**; 2003, Phillips, S. J., Whisnant, J. P. *Hypertension and stroke. In: Laragh JH, Brenner BM, Editors. Hypertension: pathophysiology, diagnosis, and management.* 2nd Ed. New York: Raven Press; 1995. s. 465–478.

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