ISSN: 1300-3755
e-ISSN 2602-3024

ARŞİV

KAYNAK TARAMA DERGİSİ

Archives Medical Review Journal

Cilt/Volume: 34 Sayı/Number: 3 Yıl/Year: 2025

Çukurova Üniversitesi Tıp Fakültesi'nin süreli bilimsel yayınıdır.
Official Journal of Cukurova University Faculty of Medicine

Archives Medical Review Journal is abstracted/indexed in Tr Dizin.
Arşiv Kaynak Tarama Dergisi Tr Dizin v*eritabanında dizinlenmektedir.*

This publication is printed on acid-free paper that meets the international standard ISO 9706:1994
(Requirements for permanence)
Bu yayının basımında ISO 9706:1994 uluslararası standartlara uygun olarak asitsiz kağıt kullanılmıştır.

https://dergipark.org.tr/tr/pub/aktd / ISSN:1300-3755 e-ISSN: 2602-3024

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal
CİLT/VOLUME 34 | SAYI/NUMBER 3 | 2025
ISSN 1300-3024

Yazışma Adresi /Correspondence Address
Ç.Ü.Tıp Fakültesi Yayın ve Dokümantasyon Kurulu
01330 Balcalı-Adana-Turkey
Telefon/Phone: +90 322 3386060-3445
E-mail: editor.aktd@gmail.com
Web site/Web sitesi: https://dergipark.org.tr/tr/pub/aktd

Yayınevi /Publisher
Çukurova Üniversitesi Basımevi
Adana-Turkey
Telefon/Phone: +90 322 3386069
Yayın Türü: Yerel Süreli Yayın
Baskı Tarihi /Printed: September /Eylül 2025
ISSN: 1300-3755
e-ISSN: 2602-3024

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

İçindekiler / Contents

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Systemic Effects of Methotrexate upon the Peripheral Nerve Tissue

Metotreksatın Periferik Sinir Dokusu Üzerindeki Sistemik Etkileri

Ozan Işık[1], Yaşar Barış Turgut[2], Sümeyra Işık[3]

[1]Department of Neurosurgery, Adnan Menderes University School of Medicine, Aydın, Türkiye
[2]Department of Internal Medicine, Aydın State Hospital, Aydın, Türkiye
[3]Department of Internal Medicine, Aydın Atatürk State Hospital, Aydın, Türkiye

ABSTRACT
Methotrexate (MTX) is a widely used oncologic drug due to its antineoplastic and anti-inflammatory effects. Although its toxic effects on the central nervous system at high doses have long been known, its effects on the peripheral nervous system are less studied in the literature. This review discusses the systemic effects of MTX on peripheral nerve tissue at histopathological, biochemical, molecular, and behavioral levels. Experimental animal studies have shown that MTX administration leads to impaired nerve conduction, reduced myelin thickness, axonal degeneration, and increased glial activity. Moreover, elevated homocysteine levels due to disrupted folate metabolism, oxidative stress, the release of pro-inflammatory cytokines, and mitochondrial dysfunction are thought to be the main mechanisms underlying MTX-induced neurotoxicity. MTX-related peripheral neuropathies are often irreversible in clinical practice, but early diagnosis and appropriate pharmacological interventions may allow for recovery. This review aims to raise awareness by compiling current data on the effects of MTX on the peripheral nervous system, both in basic science and clinical applications.
Keywords: Drug toxicity, methotrexate, myelopathy, peripheral nerve ınjuries, neurotoxicity.

ÖZET
Metotreksat (MTX), hem antineoplastik hem de antiinflamatuvar etkileri nedeniyle yaygın olarak kullanılan bir onkolojik ilaçtır. Yüksek dozlarda kullanıldığında merkezi sinir sistemi üzerinde toksik etkiler gösterebildiği uzun süredir bilinmesine rağmen, periferik sinir sistemi üzerindeki etkileri literatürde daha az araştırılmıştır. Bu derlemede, MTX'in periferik sinir dokusu üzerine olan sistemik etkileri histopatolojik, biyokimyasal, moleküler ve davranışsal düzeylerde ele alınmıştır. Deneysel hayvan çalışmalarında, MTX uygulamasının sinir iletiminde bozulma, miyelin kalınlığında azalma, aksonal dejenerasyon ve glial aktivitede artışa yol açtığı gösterilmiştir. Ayrıca folat metabolizmasının bozulmasıyla artan homosistein seviyeleri, oksidatif stres, proinflamatuvar sitokinlerin salınımı ve mitokondriyal disfonksiyonun, MTX'e bağlı nörotoksisitenin altında yatan başlıca mekanizmalar olduğu düşünülmektedir. MTX ile ilişkili periferal nöropatiler klinikte çoğu zaman geri dönüşsüz olmakla birlikte, erken tanı ve uygun farmakolojik müdahalelerle iyileşme mümkün olabilmektedir. Bu derleme, MTX'in periferik sinir sistemi üzerindeki etkilerine dair güncel verileri bir araya getirerek, hem temel bilim hem de klinik uygulamalar açısından farkındalık yaratmayı amaçlamaktadır.
Anahtar kelimeler: İlaç toksisitesi, metotreksat, miyelopati, periferik sinir yaralanmaları, periferik nöropatiler, nörotoksisite.

Introduction

Methotrexate (MTX) is one of the folate antagonists, an antimetabolite that inhibits the enzyme dihydrofolate reductase, disrupting DNA synthesis, repair, and cellular replication. It is widely used in chemotherapy protocols for various malignancies, as well as in autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis[1,2]. Despite its clinical efficacy, it is known that MTX can cause various neurotoxic side effects in the central and peripheral nervous systems[1]. These neurotoxic effects can present in a wide

Correspondence Address / Yazışma Adresi
Ozan Işık, Adnan Menderes University School of Medicine, Department of Neurosurgery, Aydın, Türkiye, e-mail: dr.ozanisik@gmail.com

2025;34(3):175-183
doi:10.17827/aktd.1679867
Geliş tarihi/ Received: 17.05.2025
Kabul tarihi/Accepted: 28.08.2025

clinical spectrum, including acute or subacute encephalopathy, demyelinating myelopathy, cranial neuropathies, epileptic seizures, cognitive dysfunction, and peripheral neuropathy. MTX-induced neurotoxicity is associated with a multifactorial pathogenesis and is influenced by variables such as the route of administration (e.g., intrathecal vs. systemic), cumulative dose, genetic polymorphisms affecting folate metabolism, and concomitant use of other neurotoxic agents[2].

Evidence on MTX effects in the PNS is fragmented and limited compared with the CNS[3-6]. Most studies rely on rodent models, while clinical evidence largely consists of case reports/series and small observational cohorts[7-11]. Marked heterogeneity exists across dose (chronic low-dose rheumatologic vs. high-dose/intrathecal oncologic), route of administration[4,12], endpoints (nerve conduction/electrophysiology, histopathology, behavioral assays), and follow-up; standardized reporting is uncommon[13-15]. The MTX-specific peripheral neuropathy phenotype—axonal vs. demyelinating, root vs. distal fiber predominance—remains insufficiently defined, and reversibility as well as long-term outcomes are uncertain[3,7]. This gap hampers early recognition, risk stratification, and the development of preventive/therapeutic strategies in clinical practice[5,16].

Our review makes this gap explicit and synthesizes the scattered evidence with a dedicated PNS focus: (i) histopathological, biochemical, and molecular effects of MTX in the PNS; (ii) findings spanning experimental models to clinical phenotypes; (iii) pathomechanisms including folate cycle disruption, homocysteine elevation, oxidative stress, mitochondrial dysfunction, and glial responses; and (iv) diagnostic, monitoring, and treatment implications. In doing so, we map the scope, quality, and blind spots of PNS-focused evidence. This review comprehensively addresses the current literature on MTX-induced neurotoxicity, considering pathophysiological mechanisms, clinical phenotypes, and experimental models.

Methotrexate and its Mechanism of Action

Methotrexate (MTX) is an antimetabolite with antifolate activity, used as both an anticancer and anti-rheumatic drug. In 1947, it was discovered that the folic acid analogue aminopterin induced remission in children with acute lymphoblastic leukemia (ALL), leading to its use. Later, researchers sought other folic acid analogues, and in 1950, MTX, also known as amethopterin, was introduced for the treatment of ALL. By 1951, it was also used for the treatment of RA and psoriasis, and in 1988, it was approved by the Food and Drug Administration (FDA) for RA treatment. While MTX is used at high doses for solid tumors and cancers, it is administered at low doses chronically for chronic autoimmune inflammatory diseases. MTX is also used in osteosarcomas, non-Hodgkin lymphomas, and some types of acute myeloblastic leukemia[17].

MTX competitively inhibits the enzyme dihydrofolate reductase (DHFR), thereby disrupting the production of tetrahydrofolate (THF). The decrease in THF synthesis leads to reduced purine nucleotide and thymidylate synthesis, which in turn decreases cell replication and DNA synthesis. Through this mechanism, MTX exerts its anticancer effects. Its anticancer efficacy is primarily cytotoxic to rapidly proliferating cells, such as lymphocytes. However, the role of MTX in RA treatment is explained differently. MTX reduces purine synthesis, leading to the accumulation of adenosine, which inhibits T cells, decreases the expression of intercellular adhesion molecules by T cells, down-regulates B cells, increases CD95 sensitivity in T cells, reduces methyltransferase activity, and decreases the binding of interleukin-1 beta to the cell surface. These anti-cytokine effects are thought to be responsible for its effectiveness in treating the autoimmune disease RA. It is recommended to be used once or twice weekly for RA treatment[18].

MTX has side effects including hepatotoxicity, intestinal toxicity, nephrotoxicity, cognitive impairment, peripheral neuropathy, axonopathy, and demyelination. These side effects may be due to folate deficiency, which disrupts purine and pyrimidine metabolism[19]. Due to these adverse effects, dose adjustment and sometimes drug discontinuation may be required. This can lead to the interruption of treatment in many patients. Neuropathy and demyelination can persist for a long time in the patient[20]. While numerous studies have been conducted on the effects of MTX on the central nervous system (CNS)[21], there is insufficient research in the literature regarding its effects on peripheral nerves. The neurotoxic effects of MTX are shown in Table-1.

Table 1. Neurotoxic Effects of MTX

Neurotoxicity	Clinical presentations
Acute (Within a few hours)	Drowsiness, mental confusion, exhaustion, impaired orientation, convulsions Chemical-induced arachnoiditis: headache, nausea, vomiting, elevated temperature, back pain, lightheadedness
Subacute (Following days to weeks)	Encephalopathy: one-sided limb weakness, impaired coordination, speech issues, epileptic seizures, confusion, mood swings Myelopathy: leg pain, altered sensation, paraplegia, bladder dysfunction
Chronic (Following months to years)	Learning disability, intellectual impairments, reduced cognitive abilities Leucoencephalopathy: disorientation, drowsiness or agitation, convulsions, lack of coordination, cognitive decline, speech difficulties, full-body paralysis, vision problems, slurred speech, coma, death

MTX:Methotrexate

Methods – Evidence Classification

We pre-specified a two-tier synthesis to avoid conflation of clinical and preclinical data. Evidence from human participants was analyzed under Clinical Evidence, while animal/ex vivo/in vitro studies were analyzed under Preclinical (Animal) Evidence. Mixed reports were split by tier. Within each tier, outcomes were harmonized by domain (clinical: neurological phenotype, NCS/EMG, imaging, longitudinal recovery; preclinical: behavioral assays, electrophysiology/nerve conduction, histopathology, and molecular readouts). Dose and route (low-dose rheumatologic vs. high-dose/intratecal oncologic; intratecal/intravenous/intraperitoneal/subcutaneous) were extracted a priori. Translational comparisons were restricted to a dedicated section.

Clinical Evidence (Human data)

MTX-induced neurotoxicity can occur due to idiosyncratic reactions or a lowered threshold for neuronal damage. MTX-induced leukoencephalopathy is a chronic side effect resulting from neuronal damage. Subacute myelopathy, another MTX side effect, progressively causes paraplegia, sensory loss, and urinary and fecal incontinence[22].

Peripheral neuropathy is commonly observed with the use of chemotherapeutic agents. As the duration and dose of chemotherapy increase, the severity of peripheral neuropathy may also intensify[10]. In the study by Yılmaz et al., increased GFAP immunoreactivity in response to MTX was associated with damage to Schwann glial cells in peripheral nerves[11]. Bax/Bcl2 genes play a role in the regulation of apoptosis[23]. The degradation of damaged mitochondria is mediated through the PINK1 and Parkin pathways. Dysfunction in these mitochondrial degradation pathways leads to toxicity and neuronal loss. Both apoptosis and mitochondrial degradation pathways are essential for the healthy functioning of cells[24]. A study reported that in MTX-treated rats, the increase in the Bax/Bcl2 ratio, indicative of an apoptotic effect, activated apoptotic pathways[11]. A study conducted between 1990 and 2021 on patients receiving MTX therapy found that 5.22% of patients developed neurotoxicity. Of those who developed neurotoxicity, 37% received intrathecal MTX, 22.2% received intravenous MTX, and 40.7% received a combination of both. Among neurotoxicity presentations, encephalopathy was the most common (69.2%), followed by encephalomyelopathy (15.4%), myelopathy (11.5%), and polyradiculopathy (3.8%). Pediatric age group, male gender, and receiving intrathecal treatment in adults and intravenous treatment in children were identified as risk factors for neurotoxicity. Brain imaging results indicated that subcortical and deep white matter were most frequently affected (54.55%), followed by the centrum semiovale (40.91%) and periventricular white matter (36.36%). Spinal involvement was seen in 37.88% of neurotoxic patients, with dorsal column lesions reported in approximately half of these cases[6].

MTX-induced neurotoxic side effects can include epileptic seizures, focal neurological deficits, stroke-like episodes, myelopathy, radiculopathy, posterior reversible encephalopathy syndrome, leukoencephalopathy, and diffuse encephalopathy[25]. MTX can damage the nervous system through astrocytosis, axon loss, and demyelination[26]. It is believed that the neurotoxic effects of MTX are due to its inhibition of dihydrofolate reductase. This inhibition raises homocysteine levels and lowers methionine levels, which in turn increases the levels of excitatory sulfur-containing amino acids and adenosine while decreasing tetrahydrobiopterin (BH4) levels. These changes lead to numerous alterations in neuronal pathways. A meta-analysis has associated peripheral neuropathy with elevated homocysteine levels[27]. In a study of diabetic patients, an increase in homocysteine levels was linked to diabetic neuropathy[28]. The increase in homocysteine and the reduction in S-adenosylmethionine (SAM) levels, which is used in myelin sheath synthesis, are thought to explain MTX's neurotoxic effects[29].

MTX disrupts purine synthesis, leading to the accumulation of adenosine[30]. The breakdown of adenosine occurs via the enzyme adenosine deaminase (ADA). Increased ADA activity has been observed in immunoinflammatory and metabolic diseases. In conditions such as myasthenia gravis, Graves' disease, RA, and systemic lupus erythematosus, serum ADA activity has been elevated. Inflammatory diseases like ectopic pregnancy, preeclampsia, inflammatory bowel disease, and gestational diabetes have also shown elevated ADA levels[31]. A study in diabetic patients identified high ADA levels as a risk factor for neuropathy. Those with high ADA levels were found to have lower nerve conduction speed[32].

Acute neurotoxic symptoms related to MTX can present as stroke[33] or transverse myelitis[34]. In pediatric patients, epileptic seizures may occur[35]. MTX-induced myelopathy can present as subacute combined degeneration (SCD), though it differs in that it does not respond to cobalamine[6]. In a study of 13 leukemia patients treated with intrathecal MTX, urinary and bowel incontinence, motor weakness, sensory loss, and dorsal column hyperintensity on MRI were observed, resembling SCD. However, normal vitamin B12 levels in these patients confirmed the differential diagnosis. In 8 patients with available data, 7 showed elevated serum homocysteine and low serum folate levels[36].

Dextromethorphan can be used for MTX-induced neurotoxicity. Dextromethorphan blocks N-methyl-D-aspartate (NMDA) receptors non-competitively and plays a protective role against the neurotoxic effects of homocysteine and other excitatory amino acids[22]. Peripheral neuropathies associated with MTX have been reported at the case-report level. In a patient with central nervous system lymphoma receiving high-dose intrathecal MTX, weakness and hyporeflexia in the right leg improved after MTX discontinuation[37].

In two patients treated with intrathecal MTX, urinary retention followed by lower limb weakness and subsequent paraplegia was observed. Electromyography (EMG) showed no F waves, and magnetic resonance imaging (MRI) revealed spinal cord involvement. The patients were diagnosed with acute lumbar polyradiculoneuropathy. Despite discontinuing MTX and adding methylprednisolone, there was no improvement in their neurological condition[7]. MRI in MTX-induced myelopathy may show dorsal hyperintensity[38]. In cerebrospinal fluid, an increase in myelin basic protein levels may be observed[39].

MTX-induced transverse myelopathy is a rare condition that can arise from intrathecal MTX therapy. In transverse myelopathy, which causes isolated spinal cord dysfunction, symptoms appear within hours or days after MTX treatment without compressive lesions. Factors that increase the risk of MTX-induced transverse myelopathy include high-dose intrathecal MTX therapy, systemic MTX treatment, active CNS disease, MTX treatment intervals of less than one week, and the use of other chemotherapeutic drugs[40]. Only about 3% of patients receiving intrathecal MTX develop transverse myelopathy[41]. MTX-induced myelopathy can affect the lumbosacral level and proximal motor roots, typically resulting in a poor prognosis. There are case reports suggesting that folic acid supplementation can improve symptoms of MTX-induced myelopathy[42].

Steroid therapy can be used to reduce vasogenic edema in MTX-induced neurotoxicity[43]. In addition to dextromethorphan, leucovorin[44] and aminophylline[45] are also used for this purpose. Various drugs have been experimentally studied to reverse MTX-induced neurotoxicity. Ketamine, with its NMDA antagonistic effect, has been tried in patients with MTX-induced neurotoxicity who require sedation[46].

The literature also mentions the occurrence of lymphoproliferative diseases in the spinal cord associated with MTX. It has been suggested that high-dose MTX can activate Epstein-Barr virus, which causes lymphoproliferative diseases through apoptotic mechanisms and B-cell transformation. Case reports have shown that discontinuation of MTX therapy leads to regression of these lymphoproliferative diseases[12,47].

Intrathecal MTX is widely used to prevent CNS relapse in ALL patients. A case report described a 31-year-old male patient with T-cell ALL who developed progressive paraplegia within days after intrathecal MTX infusion. Pathological examinations revealed transverse necrosis and extensive macrophage infiltration in the thoracic spinal cord, along with subpial vacuolar degeneration in the cerebellum and lumbar regions, and loss of cerebral white matter[48]. Additionally, MTX's effects on folate metabolites, particularly 5-methyl-THF and SAM, impair myelination and cause degeneration in both the CNS and peripheral nervous system[49]. Furthermore, MTX's direct toxic effects on endothelial cells can lead to damage of the vessel walls, allowing the drug to penetrate deeply into the CNS parenchyma, resulting in necrosis and vacuolar degeneration[50]. If not treated, this toxicity can lead to rapid neurological symptoms and permanent motor loss. In this case, a diagnosis of MTX-induced transverse myelopathy was made[48], and this side effect occurs in approximately 3% of cases[51]. High-dose steroids and folic acid analogs are recommended in the presence of this side effect[48].

MTX inhibits the DHFR enzyme, lowering THF levels and disrupting the synthesis of essential compounds for DNA and RNA synthesis, such as purines and thymidine. This reduction in THF production disrupts the homocysteine-methionine cycle, leading to elevated homocysteine levels and decreased methionine levels[52]. In healthy individuals, cerebrospinal fluid (CSF) homocysteine levels are typically ≤0.5 nmol/mL, but after systemic MTX treatment, these levels can rise to 1.0 nmol/mL[53]. Elevated homocysteine levels and decreased methionine activate excitatory mechanisms through NMDA receptors, which contribute to neurotoxicity[54]. Another component of MTX toxicity is the dysfunction of astrocytes, which leads to axonal loss and demyelination, particularly in the dorsal columns of the spinal cord[55]. Clinical signs of SCD in patients receiving high-dose systemic and intrathecal MTX therapy include progressive paraplegia, sensory loss, and neurogenic bladder. Genetic factors, such as polymorphisms in methylenetetrahydrofolate reductase (MTHFR), may modulate sensitivity to MTX neurotoxicity, but their role remains unclear. Despite being considered irreversible, MTX-induced myelopathy has shown improvement with early intervention, including folate supplementation, SAM, dextromethorphan, and intensive rehabilitation therapy[56]. These findings highlight the complexity of MTX neurotoxicity and the need for developing optimal therapeutic strategies to mitigate these effects through specific molecular and genetic mechanisms.

Peripheral neuropathy associated with subcutaneous MTX administration has also been reported. In a 70-year-old female patient with RA, damage to the median nerve was observed after subcutaneous MTX injection, which improved with pregabalin treatment[57]. In a study by Zhou et al. in rats, short-term MTX treatment led to a significant increase in calcitonin gene-related peptide (CGRP)-positive nerve fibers in the tibial periosteum, which was parallel to the development of pain behaviors triggered by touch in the following days. Mechanical allodynia, assessed using von Frey tests, was significantly increased in the MTX group, suggesting that MTX lowered the pain threshold at peripheral nerve endings. These effects may be due to MTX's disruption of folate metabolism, increasing homocysteine levels, triggering neuroinflammation, and causing hyperexcitability in sensory neurons. Additionally, MTX may promote the remodeling of sensory fibers in tissues such as the periosteum, increasing sensitivity to painful stimuli. These findings suggest that MTX can cause neuropathy in the peripheral nervous system through both direct toxic and indirect inflammatory mechanisms, and that chemotherapy-induced pain may be linked not only to bone damage but also to increased sensory innervation[10].

Preclinical (Animal) Evidence

In a 2024 study, rats were divided into four groups: control, MTX, agmatine, and MTX+agmatine. Rats received 37.5 mg/kg/week of intraperitoneal MTX for 3 weeks. The study found that MTX-treated rats exhibited longer escape times in the water maze test, reduced time spent in the quadrant, fewer frames crossed in the open field test, increased nociceptive latencies, and decreased nerve conduction speed and sciatic function index. Histological examination of the sciatic nerve in the MTX group revealed a decrease

in myelin thickness and axon diameter. Additionally, increased glial fibrillary acidic protein (GFAP) immunoreactivity was observed in the sciatic nerve of the MTX-treated rats. Western blot analysis showed increased Bax/Bcl2 protein expression, but no changes in Parkin expression. The MTX+agmatine group showed significant improvement in the peripheral neuropathy caused by MTX. The prolonged escape times in the water maze test suggest that MTX also affected the rats' learning and memory abilities[11].

BH4 is essential for normal brain maturation. A study in rats with congenital heart disease showed an association between reduced BH4 levels and delayed brain maturation[58]. Other studies reported that exogenous BH4 administration corrected hypoxia-induced delays in myelination, improved sensorimotor coordination, and reduced apoptosis in white matter[59]. BH4 is also required for the hydroxylation of phenylalanine, tyrosine, and tryptophan, thus influencing dopamine and serotonin synthesis. Due to the biochemical reactions induced by MTX, the reduction in dopamine and serotonin levels leads to symptoms such as hypokinesia, body hypotonia, difficulty swallowing, oculogyric crisis, limb rigidity, and recurrent hyperpyrexia[60].

In an experimental rat study investigating the histological, immunohistochemical, and biochemical effects of MTX, hippocampal structural damage, degeneration of pyramidal cell layers, cerebellar congestion, and Purkinje cell degeneration were observed. Increased caspase-3 expression in the hippocampus and cerebellum was also noted[61]. Caspase-3 is known for its pro-apoptotic effect and for marking the irreversible point of apoptosis[62]. Furthermore, GFAP immunoreactivity was increased in the hippocampus and cerebellum of MTX-treated rats[42]. GFAP, a cell skeleton filament, appears in the CNS following cell damage or cell death[63].

A study examining the effects of MTX on peripheral nerves using carvacrol and pomegranate in rats found increased levels of total oxidants, MDA, Tumor necrosis factor (TNF)-alpha, and interleukin-1-beta, while total antioxidant levels were decreased in the sciatic nerves of MTX-treated rats[64]. TNF-alpha and interleukin-1-beta are pro-inflammatory cytokines associated with cell death and inflammation[65]. It is believed that MTX has anti-inflammatory effects at low doses, while at higher doses, it triggers the release of pro-inflammatory cytokines, leading to neurotoxicity[66].

Previous studies have shown that MTX administration leads to oxidative stress in various tissues, including the sciatic nerve, spinal cord, and brainstem[61,64,67]. MTX-associated neurotoxicity is primarily linked to the increased production of reactive oxygen species (ROS), leading to lipid peroxidation and cellular damage. The role of oxidative stress in MTX-induced neurotoxicity has been highlighted in studies investigating potential neuroprotective effects of antioxidants like caffeic acid phenethyl ester (CAPE). Known for its antioxidant properties, CAPE significantly reduced levels of malondialdehyde (MDA), a marker of oxidative stress, and improved the activity of antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT) in neuronal tissues. These findings suggest that MTX-induced damage could be alleviated with CAPE, making it a promising agent to reduce MTX-related peripheral nerve toxicity[67].

In a study by Pranaya et al. (2021), the effects of *Passiflora incarnata* and pregabalin were evaluated in MTX-induced neuropathy. MTX was administered to rats to induce peripheral neuropathy, leading to behavioral changes such as increased thermal hyperalgesia (sensitivity to heat) and cold allodynia (pain from non-painful stimuli). Pain sensitivity was elevated in the MTX group. Biochemical markers of oxidative stress, including TBARS (a marker of lipid peroxidation), GSH (reduced glutathione), and calcium levels, were measured in the sciatic nerve tissue. MTX treatment increased TBARS and calcium levels while decreasing GSH levels. *Passiflora incarnata* treatment reversed these changes, demonstrating the plant's antioxidant and neuroprotective properties. Histopathological analysis of the sciatic nerve after MTX treatment revealed axonal degeneration and swelling, but treatment with *Passiflora incarnata* significantly reduced these pathological changes, showing a protective effect on the nerve tissue[68].

In a study by Scholz et al. (2008), it was shown that at one-fiftieth of the dose that induces neurotoxicity, the spinal microglial activation and subsequent neuropathic pain behaviors following peripheral nerve injury could be suppressed. In this study, rats with a spinal nerve injury model were given low-dose intrathecal MTX, which significantly reduced microglial activity in the dorsal horn, suppressed p38 mitogen-activated protein kinase (MAPK) phosphorylation, and reversed pain behaviors such as mechanical and cold

allodynia. The study emphasized that this effect was observed only when treatment was initiated early and had no significant impact on microglial activation when applied later. These findings suggest that MTX might play a role not only in its neurotoxic effects but also in neuropathic processes due to its immune-modulatory potential[69].

Translational Bridge

We confine cross-tier interpretation to this section. Convergence: Across tiers, folate-cycle disruption (↑homocysteine; ↓methylation capacity), oxidative stress, glial responses, and axonal/myelin injury recur. Divergence: Clinical phenotypes cluster around intrathecal/high-dose exposures with variable reversibility, whereas preclinical models emphasize reproducible molecular and glial signatures under controlled dosing. Bridging metrics: standardized NCS/EMG endpoints, explicit reporting of dose/route and time-to-onset, and homocysteine/S-adenosylmethionine panels may improve translation. A potential bidirectional window exists wherein low-dose regimens modulate neuroimmune pathways (e.g., microglia), while higher doses drive toxicity reinforcing dose timing context in clinical decision-making.

Conclusion

MTX, with its potent therapeutic effects, also draws attention due to its toxic effects on the nervous system. As presented in this review, MTX-induced neurotoxicity is not only related to the suppression of folate metabolism but also involves multifactorial mechanisms such as oxidative stress, pro-inflammatory responses, mitochondrial dysfunction, glial cell activation, and apoptosis. These effects in the peripheral nervous system can lead to significant changes both at the behavioral level as well as histopathologically and molecularly. The findings suggesting that MTX may suppress microglial activation at low doses to prevent the development of neuropathic pain imply that the drug's immunomodulatory effects could create a delicate balance between toxicity and therapy, depending on the dose. Therefore, when planning MTX therapy, the patient's neurological risk profile should be considered, and careful monitoring is essential, especially with high doses and intrathecal administration. Future studies will contribute to a better understanding of these mechanisms, aiding in the development of targeted therapies to prevent or reverse MTX-induced neurotoxicity.

References

1. Pannu AK. Methotrexate overdose in clinical practice. Curr Drug Metab. 2019;20:714-9.
2. Gaies E, Jebabli N, Trabelsi S, Salouage I, Charfi R, Lakhal M et al. Methotrexate side effects: review article. J Drug Metab Toxicol. 2012;3:1-5.
3. Mateos MK, Marshall GM, Barbaro PM, Quinn MCJ, George C, Mayoh C et al. Methotrexate-related central neurotoxicity: clinical characteristics, risk factors and genome-wide association study in children treated for acute lymphoblastic leukemia. Haematologica. 2022;107:635-43.
4. Staff NP, Grisold A, Grisold W, Windebank AJ. Chemotherapy-induced peripheral neuropathy: A current review. Ann Neurol. 2017;81:772-81.
5. Burgess J, Ferdousi M, Gosal D, Boon C, Matsumoto K, Marshall A et al. Chemotherapy-Induced Peripheral Neuropathy: Epidemiology, Pathomechanisms and Treatment. Oncol Ther. 2021;9:385-450.
6. Apiraksattayakul N, Jitprapaikulsan J, Sanpakit K, Kumutpongpanich T. Potential neurotoxicity associated with methotrexate. Sci Rep. 2024;14:18548.
7. Montejo C, Navarro-Otano J, Mayà-Casalprim G, Campolo M, Casanova-Mollá J. Acute lumbar polyradiculoneuropathy as early sign of methotrexate intrathecal neurotoxicity: Case report and literature review. Clin Case Rep. 2019;7:638-43.
8. Xu E, Thomas S, Habibi B. Intrathecal Methotrexate-Induced Lumbosacral Polyradiculopathy: A Case Report. Pain Med Case Rep. 2024;8:31-5.
9. Lee HS, Jung HJ, Park JE. A Case of Peripheral Neuropathy Combined with Leukoencephalopathy after Injection with Intrathecal Methotrexate and Vincristine. Blood. 2007;110:4348.
10. Zhou FH, Yu Y, Zhou XF, Xian CJ. Methotrexate chemotherapy triggers touch-evoked pain and increased CGRP-positive sensory fibres in the tibial periosteum of young rats. Bone. 2015;73:24-31.
11. Yılmaz HF, & Girit ÖB. Agmatine Administration Alleviates Nerve Damage and Improves Nerve Function in Methotrexate Induced Peripheral Neuropathy in Rats. Meandros Medical And Dental Journal. 2024;25:316-35.
12. Sugimoto T, Ishikawa R, Abe T, Ohno N, Tazuma T, Giga M et al. Brachial plexus neuropathy induced by methotrexate-associated lymphoproliferative disorder in a patient with rheumatoid arthritis. Neurology and Clinical Neuroscience. 2021;9:233-6.
13. Haryani H, Fetzer SJ, Wu CL, Hsu YY. Chemotherapy-Induced Peripheral Neuropathy Assessment Tools: A Systematic Review. Oncol Nurs Forum. 2017;44:E111-23.

14. Li T, Park SB, Battaglini E, King MT, Kiernan MC, Goldstein D et al. Assessing chemotherapy-induced peripheral neuropathy with patient reported outcome measures: a systematic review of measurement properties and considerations for future use. Qual Life Res. 2022;31:3091-107.
15. Molassiotis A, Cheng HL, Lopez V, Au JSK, Chan A, Bandla A et al. Are we mis-estimating chemotherapy-induced peripheral neuropathy? Analysis of assessment methodologies from a prospective, multinational, longitudinal cohort study of patients receiving neurotoxic chemotherapy. BMC Cancer. 2019;19:132.
16. Jordan B, Margulies A, Cardoso F, Cavaletti G, Haugnes HS, Jahn P et al. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. Ann Oncol. 2020;31:1306-19.
17. Hamed KM, Dighriri IM, Baomar AF, Alharthy BT, Alenazi FE, Alali GH et al. Overview of Methotrexate Toxicity: A Comprehensive Literature Review. Cureus. 2022;14:e29518.
18. Zhao Z, Hua Z, Luo X, Li Y, Yu L, Li M et al. Application and pharmacological mechanism of methotrexate in rheumatoid arthritis. Biomed Pharmacother. 2022;150:113074.
19. Turesson C, Matteson EL. Genetics of rheumatoid arthritis. Mayo Clin Proc. 2006;81:94-101.
20. Kinder AJ, Hassell AB, Brand J, Brownfield A, Grove M, Shadforth MF. The treatment of inflammatory arthritis with methotrexate in clinical practice: treatment duration and incidence of adverse drug reactions. Rheumatology (Oxford). 2005;44:61-6.
21. Vezmar S, Becker A, Bode U, Jaehde U. Biochemical and clinical aspects of methotrexate neurotoxicity. Chemotherapy. 2003;49:92-104.
22. Fustino NJ, Juhl K, Leister J. Dextromethorphan Administration on Day 0 and Day 7 for Secondary Prevention of Methotrexate-induced Neurotoxicity in Childhood Acute Lymphoblastic Leukemia: A Retrospective Case Series. J Pediatr Hematol Oncol. 2021;43:e284-7.
23. Lopez A, Reyna DE, Gitego N, Kopp F, Zhou H, Miranda-Roman MA et al. Co-targeting of BAX and BCL-XL proteins broadly overcomes resistance to apoptosis in cancer. Nat Commun. 2022;13:1199.
24. Li J, Yang D, Li Z, Zhao M, Wang D, Sun Z et al. PINK1/Parkin-mediated mitophagy in neurodegenerative diseases. Ageing Res Rev. 2023;84:101817.
25. Mshaymesh S. Neurotoxic effects of the chemotherapeutic drug "methotrexate": a literature review. Ann Med Surg (Lond). 2024;87:1394-405.
26. Vazi EPG, Holanda F, Santos NA, Cardoso CV, Martins MFM, Bondan EF. Short-term systemic methotrexate administration in rats induces astrogliosis and microgliosis. Res Vet Sci. 2021;138:39-48.
27. Stein J, Geisel J, Obeid R. Association between neuropathy and B-vitamins: A systematic review and meta-analysis. Eur J Neurol. 2021;28:2054-64.
28. Lv N, Jia L, Liu F, Cheng L, Liu F, Kuang J et al. Elevated circulating homocysteine concentrations delayed nerve conduction velocity and increase the risk of diabetic kidney disease in patients with type 2 diabetes. Front Endocrinol (Lausanne). 2024;15:1451758.
29. Lahoti A, k Das P, Mohapatra S, Naik S, Panigrahi A, & Bhuyan B. Methotrexate (MTX) Induced Leukoencephalopathy (LE) and Relation of Vitamin B12, Folate and/or Homocysteine Levels with MTX Toxicity: A Prospective Study. Blood. 2021;138:4374.
30. Bhagavatham SKS, Potikuri D, & Sivaramakrishnan V. Adenosine deaminase and cytokines associated with infectious diseases as risk factors for inflammatory arthritis and methotrexate as a potential prophylactic agent. Medical Hypotheses. 2022;159:110751.
31. Gao ZW, Wang X, Zhang HZ, Lin F, Liu C, Dong K. The roles of adenosine deaminase in autoimmune diseases. Autoimmun Rev. 2021;20:102709.
32. Yu C, Zhuang L, Xu F, Zhao LH, Wang XH, Wang CH et al. Increased levels of serum adenosine deaminase and increased risk of diabetic peripheral neuropathy in type 2 diabetes. Front Endocrinol (Lausanne). 2022;13:997672.
33. López-De Suso D, García-Salido A, Andión-Catalán M, Leoz-Gordillo I, Lassaleta-Atienza Á, Sirvent-Cerdá S. Methotrexate-induced stroke-like neurotoxicity: Case report, 8 years of experience, and literature review. Pediatr Blood Cancer. 2022;69:e29627.
34. Levin G, Chill HH, Rottenstreich A. Transverse myelitis following methotrexate treatment of ectopic pregnancy: a case report. Eur J Contracept Reprod Health Care. 2017;22:476-8.
35. Pinnix CC, Chi L, Jabbour EJ, Milgrom SA, Smith GL, Daver N et al. Dorsal column myelopathy after intrathecal chemotherapy for leukemia. Am J Hematol. 2017;92:155-60.
36. Santangelo A, Bartolini E, Nuzzi G, Foiadelli T, Michev A, Mina T et al. The Clinical Impact of Methotrexate-Induced Stroke-Like Neurotoxicity in Paediatric Departments: An Italian Multi-Centre Case-Series. Front Neurol. 2022;13:920214.
37. El Cheikh Ali I, Ghasoub R, Al Azawi S. High Dose Methotrexate Associated with Polyneuropathy in Adult with Primary Central Nervous System Lymphoma: Case Report. Int J Pharm. 2015;5:335-8.
38. Cachia D, Kamiya-Matsuoka C, Pinnix CC, Chi L, Kantarjian HM, Cortes JE et al. Myelopathy following intrathecal chemotherapy in adults: a single institution experience. J Neurooncol. 2015;122:391-8.
39. Chen YC, Sheen JM, Wang SC, Hsu MH, Hsiao CC, Chang KA et al. Methotrexate Neurotoxicity Is Related to Epigenetic Modification of the Myelination Process. Int J Mol Sci. 2021;22:6718.
40. Pan Y, Wang C, Wang H, Tao Q, Xiong S, Zhai Z. Transverse myelopathy occurring with intrathecal administration of methotrexate and cytarabine chemotherapy: A case report. Oncol Lett. 2016;11:4066-8.
41. Teh HS, Fadilah SA, Leong CF. Transverse myelopathy following intrathecal administration of chemotherapy. Singapore Med J. 2007;48:e46-9.

42. Rodrigues PGB, Lima TT, Duarte FB, Nóbrega PR. Myelopathy associated with intrathecal methotrexate. Pract Neurol. 2022;22:141-4.
43. Awad H, & Ali UF. Management of methotrexate toxicity. Journal of advanced Biomedical and Pharmaceutical Sciences. 2021;4:32-6.
44. Jiang R, Mei S, Zhao Z. Leucovorin (folinic acid) rescue for high-dose methotrexate: A review. J Clin Pharm Ther. 2022;47:1452-60.
45. Razi W, Haque AU, Sadiq H, Ullah R, Jabbar N, Mirza S. Safety and Efficacy of Aminophylline in Intrathecal Methotrexate-related Neurological Toxicity in Large Pediatric Oncology Centre. J Coll Physicians Surg Pak. 2021;31:481-4.
46. Ilahi Z, Janardhan S, Dave M, Khariton M, Feuer P, Venkataraman A et al. Ketamine as an Adjunct for Treatment of Methotrexate-induced Neurotoxicity. J Pediatr Hematol Oncol. 2022;44:e512-3.
47. Yamaguchi Y, Morimoto T, Toda Y, Tsukamoto M, Yoshihara T, Hirata H et al. The first case of methotrexate-associated lymphoproliferative disorder in the sacrum: a case report. BJR Case Rep. 2024;10:uaae002.
48. Tariq H, Gilbert A, Sharkey FE. Intrathecal Methotrexate-Induced Necrotizing Myelopathy: A Case Report and Review of Histologic Features. Clin Med Insights Pathol. 2018;11:1179555718809071.
49. Linnebank M, Pels H, Kleczar N, Farmand S, Fliessbach K, Urbach H et al. MTX-induced white matter changes are associated with polymorphisms of methionine metabolism. Neurology. 2005;64:912-3.
50. Shibutani M, Okeda R. Experimental study on subacute neurotoxicity of methotrexate in cats. Acta Neuropathol. 1989;78:291–300.
51. Teh HS, Fadilah SAW, Leong CF. Transverse myelopathy following intrathecal administration of chemotherapy. Singapore Med J. 2007;48:e46–9.
52. Rushworth D, Mathews A, Alpert A, Cooper LJ. Dihydrofolate Reductase and Thymidylate Synthase Transgenes Resistant to Methotrexate Interact to Permit Novel Transgene Regulation. J Biol Chem. 2015;290:22970-6.
53. Murata KY, Maeba A, Yamanegi M, Nakanishi I, Ito H. Methotrexate myelopathy after intrathecal chemotherapy: a case report. J Med Case Rep. 2015;9:135.
54. Poddar R, Paul S. Homocysteine-NMDA receptor-mediated activation of extracellular signal-regulated kinase leads to neuronal cell death. J Neurochem. 2009;110:1095-106.
55. Shao Y, Tan B, Shi J, Zhou Q. Methotrexate induces astrocyte apoptosis by disrupting folate metabolism in the mouse juvenile central nervous system. Toxicol Lett. 2019;301:146-56.
56. Dukenik DB, Soong D, Li W, Madarang E, Watts J, & Taylor J. Methotrexate-induced subacute combined degeneration in acute lymphoblastic leukemia with CNS relapse may be reversible. Hemato. 2023;4:311-20.
57. Rekib Sacaklidir. Median Nerve Damage After Methotrexate Injection. ARC Journal of Orthopedics. 2024;9:1-3.
58. Sawada M, Hirata Y, Arai H, Iizuka R, Nagatsu T. Tyrosine hydroxylase, tryptophan hydroxylase, biopterin, and neopterin in the brains of normal controls and patients with senile dementia of Alzheimer type. J Neurochem. 1987;48:760-4.
59. Romanowicz J, Leonetti C, Dhari Z, Korotcova L, Ramachandra SD, Saric N et al. Treatment with Tetrahydrobiopterin Improves White Matter Maturation in a Mouse Model for Prenatal Hypoxia in Congenital Heart Disease. J Am Heart Assoc. 2019;8:e012711.
60. Sabry NC, Michel HE, & Menze ET. Chemotherapy and cognitive function: comprehensive review on methotrexate-induced chemobrain. Archives of Pharmaceutical Sciences Ain Shams University. 2023;7:402-20.
61. Ahmed ZSO, Hussein S, Ghandour RA, Azouz AA, El-Sakhawy MA. Evaluation of the effect of methotrexate on the hippocampus, cerebellum, liver, and kidneys of adult male albino rat: Histopathological, immunohistochemical and biochemical studies. Acta Histochem. 2021;123:151682.
62. Khalifa MMA, Bakr AG, Osman AT. Protective effects of phloridzin against methotrexate-induced liver toxicity in rats. Biomed Pharmacother. 2017;95:529-35.
63. Žurek J. Biomarkers in traumatic brain injury. In Essentials of Neuroanesthesia Academic Press. 2017;587-91.
64. Celik F, Gocmez C, Bozkurt M, Kaplan I, Kamasak K, Akil E et al. Neuroprotective effects of carvacrol and pomegranate against methotrexate-induced toxicity in rats. Eur Rev Med Pharmacol Sci. 2013;17:2988-93.
65. Pineau I, Lacroix S. Proinflammatory cytokine synthesis in the injured mouse spinal cord: multiphasic expression pattern and identification of the cell types involved. J Comp Neurol. 2007;500:267-85.
66. Kim YJ, Song M, Ryu JC. Inflammation in methotrexate-induced pulmonary toxicity occurs via the p38 MAPK pathway. Toxicology. 2009;256:183-90.
67. Uzar E, Koyuncuoğlu HR, Yılmaz HR, Uz E, Songar A, Sahin O et al. Ameliorating role of caffeic acid phenethyl ester (CAPE) against methotrexate-induced oxidative stress in the sciatic nerve, spinal cord and brain stem tissues of rats. Turkish Journal of Neurology. 2010;16:12-20.
68. Pranaya P, & Athilli L. Behavioral and Pharmacological Characteristics of Passiflora Incarnata On Methotrexate-Induced Peripheral Neuropathy In Rats. Nat Volatiles & Essent Oils. 2021;8:5526-36.
69. Scholz J, Abele A, Marian C, Häussler A, Herbert TA, Woolf CJ et al. Low-dose methotrexate reduces peripheral nerve injury-evoked spinal microglial activation and neuropathic pain behavior in rats. Pain. 2008;138:130-42.

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Exhaled Carbon Monoxide Measurement Errors: A Systematic Review of Causes and Solutions

Ekshale Edilen Karbon Monoksitin Ölçüm Hataları: Nedenler ve Çözümlerin Sistematik Bir Derlemesi

İzzet Fidancı[1], Özlem Kızıltaş[2]

[1]Hacettepe University, Faculty of Medicine, Department of Family Medicine, Ankara, Türkiye
[2]Seyhan Health Directorate, Adana, Türkiye

ABSTRACT
The review will discuss the various etiologies that lead to a faulty measurement using exhaled carbon monoxide devices, widely utilized in clinical settings, especially with smoking-cessation programs and the assessment of exposure to carbon monoxide (CO). These devices, though of paramount importance in monitoring CO levels, bear errors in measurement that may be immense in significance to clinical decisions and patient outcomes. Some of the other common reasons for faulty readings include calibration errors, different sensor technologies, humidity and temperature, poor breath sampling on the part of the users, and the ageing of devices. Even with an increase in the sensitivity of sensors, their performance can be influenced by both external and internal factors. Periodic recalibration of the devices, their proper use, and updating with advanced technologies are stressed in the review for error-free results. This would aid in overcoming most the problems with exhaled CO measurement devices and enhance their reliability, since continuous and accurate data would be provided for both clinical and emergency use.
Keywords: Carbon monoxide, breath tests, smoking, bias, outcome measurement errors

ÖZET
Klinik ortamlarda, özellikle sigarayı bırakma programları ve karbon monoksit (CO) maruziyetinin değerlendirilmesinde yaygın olarak kullanılan ekshale edilen karbon monoksit cihazları kullanılarak yapılan hatalı ölçümlere yol açan çeşitli etiyolojiler bu derlemede ele alınacaktır. Bu cihazlarda, CO seviyelerinin izlenmesinde büyük önem taşısa da klinik kararlar ve hasta sonuçları açısından büyük önem taşıyabilecek ölçüm hataları olabilmektedir. Hatalı ölçümlerin yaygın nedenlerinden bazıları kalibrasyon hataları, farklı sensör teknolojileri, nem ve sıcaklık, kullanıcılar tarafından kötü nefes örneklemesi ve cihazların eskimesidir. Sensörlerin hassasiyetinde artış olsa bile, performansları hem dış hem de iç faktörlerden etkilenebilir. Hatasız sonuçlar için incelemede cihazların periyodik olarak yeniden kalibre edilmesi, uygun şekilde kullanılması ve gelişmiş teknolojilerle güncellenmesi vurgulanmaktadır. Bu, ekshale edilen CO ölçüm cihazlarıyla ilgili sorunların çoğunun üstesinden gelinmesine yardımcı olacak ve sürekli ve doğru veriler hem klinik hem de acil kullanım için sağlanacağından güvenilirliklerini artıracaktır.
Anahtar kelimeler: Karbon monoksit, nefes testleri, sigara içme, önyargı, sonuç ölçüm hataları

Introduction

The Exhalation Breath Test provides a non-invasive and practical method of assessing human health. This test is based on the principle of analyzing various gaseous and dissolved substances present in the breath, which vary according to the physical environment, dietary habits and health status of the individual. The study of these components in the breath can be used to diagnose diseases of the lungs and other organs or to monitor the effectiveness of drug treatments. Carbon monoxide (CO) is a common gas produced by organic combustion and is also produced naturally in the body as a by-product of metabolism. At high concentrations it can bind to hemoglobin and inhibit oxygen transport, while at low levels it may play a role in cellular homeostasis and vascular function. Exhaled CO (eCO) has been studied as a biomarker for several inflammatory conditions, including smoking and lung disease[1].

Correspondence Address / Yazışma Adresi
İzzet Fidancı, Hacettepe University, Faculty of Medicine, Department of Family Medicine, Ankara, Türkiye e-mail: izzetfidanci@gmail.com

2025;34(3):184-194
doi:10.17827/aktd.1732832
Geliş tarihi/ Received: 02.07.2025
Kabul tarihi/Accepted: 01.09.2025

Many devices called exhaled carbon monoxide meters are available for the detection of smoking and carbon monoxide exposure. These devices play a critical role in smoking cessation programs, with an emphasis on the assessment of people-smoking or not-based on their carbon monoxide (CO) levels. They are also used in emergent situations such as fire exposures and carbon monoxide poisoning. Inaccurate measurements may adversely affect clinical decisions leading to inaccurate assessment of patients [2-5].

There are many factors that contribute to the incorrect results from CO measuring devices. These include calibration errors, the use of different technologies within the devices, conditions of the setting of exposure, user errors, and aging of devices [2,3]. Appropriately accurate calibration of the devices, their use under appropriate conditions, and updating them in accordance with new technologies are vital in obtaining accurate results [4,5].

While sensing has improved with the advent of technology, there are many causes externally and internally which affect the measurement accuracy of such devices. Therefore, this review will completely address the causes of inaccurate measurements in carbon monoxide measuring devices and will reveal how these errors can be prevented.

Unlike previous reports that have primarily focused on isolated technical aspects or device-specific performance, this systematic review provides an integrated perspective by synthesizing technological, environmental, user-related, and clinical factors together. In doing so, it offers a comprehensive framework that clarifies how these multiple sources of error interact and presents practical recommendations that go beyond the scope of earlier studies.

Materials and Methods

The review was done in relation to the determination of causes of inaccurate measurements by exhaled carbon monoxide meters. A full description of data sources and methods used is provided below.

Data Sources

Information was sourced from scientific databases: PubMed, Google Scholar, Cochrane, Web of Science, and ResearchGate[6-10]. These databases have the most updated and reliable sources on research concerning the accuracy and reliability of medical devices. Studies reviewed ranged from technological development in carbon monoxide measuring devices to user errors, environmental factors, device calibration problems, and sensor error effects.

- Google Scholar: A search for comprehensive studies on the factors affecting exhaled CO meters' performance.
- PubMed was used to identify reliable articles and reports regarding clinical application of the devices.
- Cochrane: Systematic reviews and meta-analyses of studies that investigated the accuracy and reliability of devices.
- The literature review related to sensor technologies, calibration requirements, and user experiences have been done by conducting both general and academic searches in Web of Science and ResearchGate.

These would include terms like "exhaled carbon monoxide measurement", "CO measurement errors", "calibration errors in CO devices", "environmental factors affecting CO measurement", and "exhaled CO sensor technology". These keywords were used to search for studies between 2010 and 2024.

Selection Criteria

The following were the selection criteria for the reviewed studies:

1. Language: The language was limited to English.
2. Year of Publication: A comprehensive search of the entire literature was conducted, and all relevant studies were systematically reviewed. The earliest publication on this topic was identified in 1994, marking the beginning of the scientific discourse in this field.

3. Type of Study: The types of studies included experimental and observational studies, systematic reviews, meta-analyses and case studies.
4. Inclusion Criteria: We focused on those studies that discussed the factors affecting device performance and described, from that perspective, the various challenges they faced.

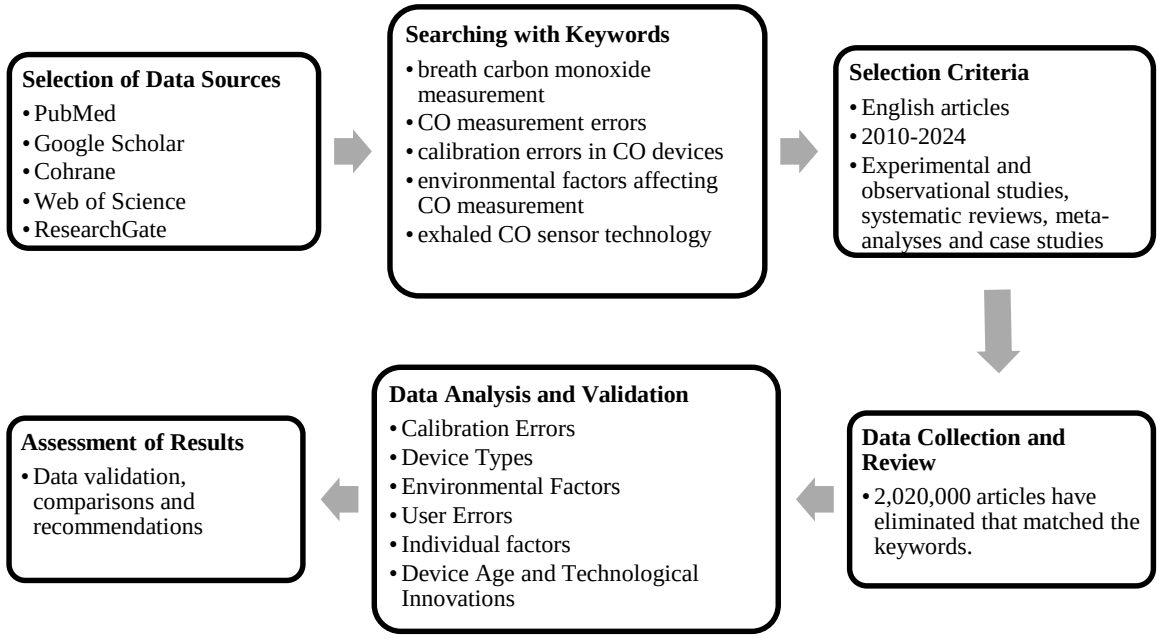


Figure 1. Flowchart of the methodology.

Study Selection and PRISMA Flow

The study selection process was carried out according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A total of 312 records were identified through electronic database searching (PubMed, Google Scholar, Cochrane Library, Web of Science, ResearchGate) and manual reference screening. After removing 54 duplicates, 258 records remained for title and abstract screening. Of these, 210 were excluded for not meeting the eligibility criteria. The full texts of 48 articles were assessed for eligibility, and 28 were excluded due to insufficient data or methodological limitations. Finally, 20 studies met the inclusion criteria and were included in the systematic review. The PRISMA flow diagram depicting this process is provided in Figure 2.

Results

Data Analysis

The retrieved studies were assessed for the following aspects:

1. Calibration Errors: Calibration errors, which arise because most of the CO measurement devices are not calibrated on a routine basis and performance degradation of sensors over time, were considered for analysis from [2,3].
2. Variations in the Types of Devices and Technologies: Performance variations between devices depending on device technologies (electrochemical sensors, infra-red sensors) were assessed from [4].
3. Ambient Environment: A review of how some environmental factors such as ambient temperature, humidity, and air pressure influence the accuracy of the devices has been done [5,11].

4. User Errors: Those made when users do not apply appropriate breathing techniques or fail to use the device in accordance with its instructions were analyzed [12].
5. Individual factors: In addition to acute and chronic diseases, medication can also affect carbon monoxide measurements [13,15-20].
6. Device Age and Technological Innovations: The aforementioned factors include lower performance from older devices compared with improvements provided by new technologies [13,14]. The major factors contributing to errors in exhaled carbon monoxide meters and some suggested solutions to reduce the errors are identified within Table 1.

Data Validation

The results were analyzed using cross-validation from different database studies. Results showed consistency in findings. Comparison of data between systematic reviews and meta-analysis to the results obtained in individual studies showed general trend findings, which pointed out several points that would go on to be considered in the use of the devices.

In the end, the review assessed causes of inaccurate measurements encountered in the exhaled CO meters from different angles and gave recommendations to minimize those errors.

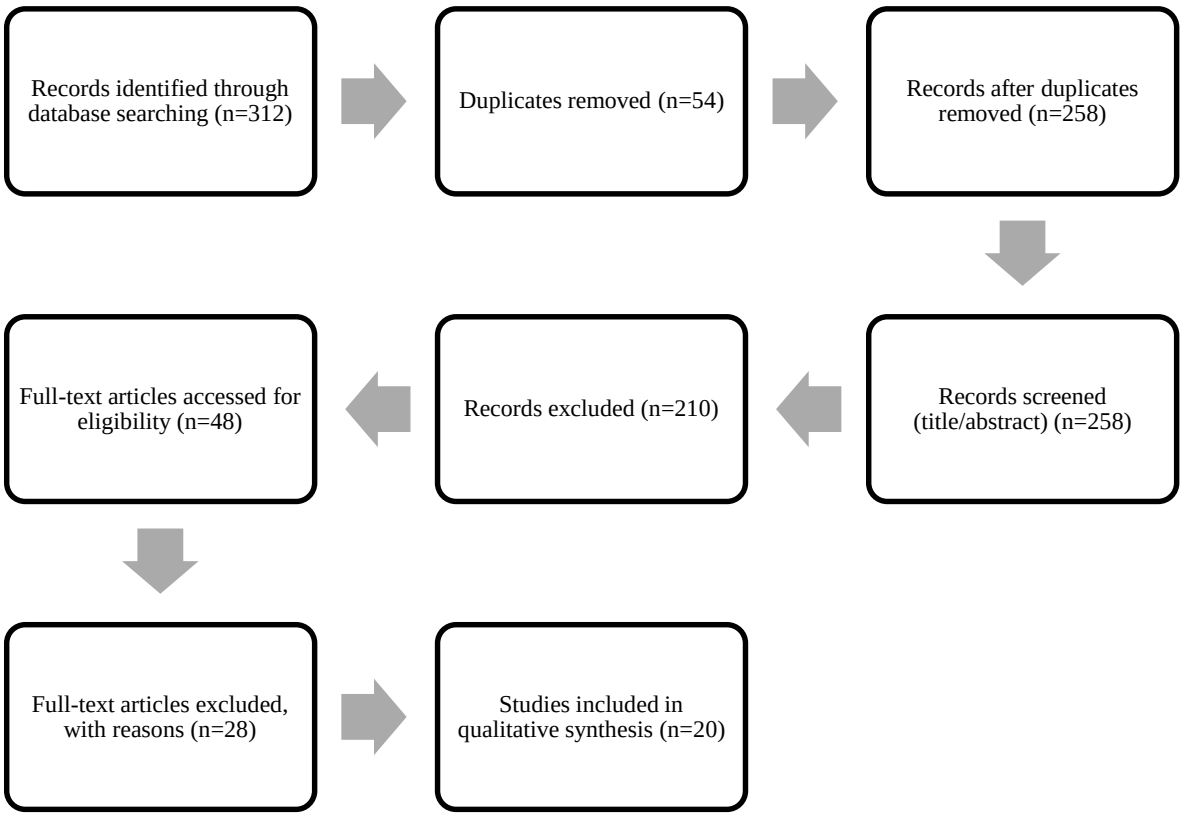


Figure 2. PRISMA flow diagram of study selection process

Table 1. Exhaled carbon monoxide measurement devices: key factors contributing to erroneous measurements

Study Reference	Sample size	Methodology	Key Findings	Device Type (Error Type)	Recommendations
Vreman et al.[2] 1994	108 Neonates	Experimental study on semiportable electrochemical instruments	Calibration of CO meters has a significant impact on measurement accuracy	Electrochemical (Calibration Errors)	Regular calibration is essential to maintain accuracy
Bailey et al.[4] 1997	23 (precision), 12 (O_2 sat.), 28 (Hb linearity) Post-op ICU and cardiac catheterization patients)	Evaluation of different sensor technologies	Significant differences found between infrared and electrochemical sensors in accuracy	Spectrophotometric, cuvette-based (Sensor Technology)	Prefer infrared sensors for higher accuracy, though costly
Olson et al.[5] 2010	16 Postmortem heart blood samples	Study on environmental impact on CO measurements	High humidity and temperature negatively affect sensor accuracy	Diametrics Medical CO-oximeter; UV spectrophotometer (Environmental Factors)	Perform tests in controlled environments to minimize errors
Sato et al.[12] 2003	Outpatients with asthma (n=161) and COPD (n=170)	User behavior analysis during CO measurement	Incorrect breathing techniques lead to inaccurate results	Electrochemical sensor-based portable CO monitor (User Errors)	Training users in proper breathing techniques is essential
Montuschi et al.[18] 2015	10 healthy nonsmokers, 12 healthy smokers, 15 ex-smoker COPD, 15 current smoker COPD (n=52)	Study on CO levels in COPD patients	Exhaled CO levels increase in respiratory infections, leading to misleading results	Electrochemical CO monitor integrated with chemiluminescence analyzer	CO levels should be interpreted cautiously in patients with respiratory infections

Discussion

In contrast to earlier publications that addressed individual sources of error separately, the present review advances the field by systematically integrating evidence across calibration, technology, environmental, and user-related domains, thereby offering a broader and more clinically applicable perspective.

Calibration Errors

Calibration is an important aspect of the instruments in making correct measurements. Unless the instruments are regularly calibrated, the sensors lose sensitivity, thus reflecting incorrect results after some period. In the study done by Vreman et al., it was shown that the calibration of the meters of CO has a great impact on their accuracy [2]. Any lack of calibration might result in the delivery of incorrect results during clinical use. This can prove hazardous during treatments and follow-up with patients. Periodic calibration of instruments should therefore be ensured according to the instructions of the manufacturer and through regular maintenance (Figure 3)[3].

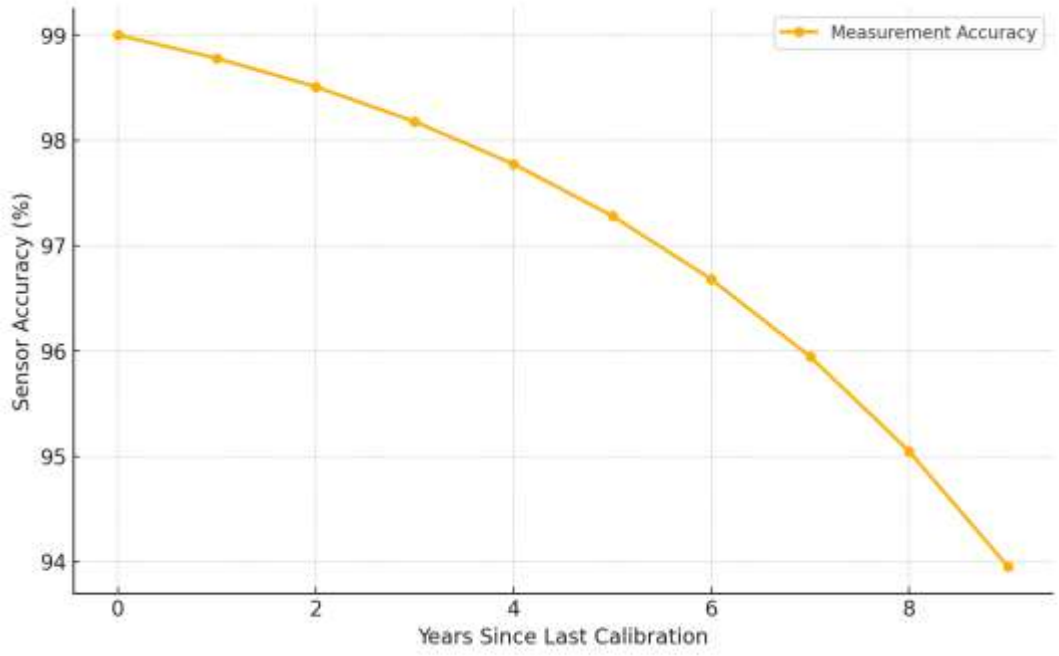


Figure 3. Effect of Calibration Errors on Measurement Accuracy

Variations in the Types of Devices and Technologies: The sensors within CO meters will also differ in type-for example, electrochemical or infra-red-and there are differences in performance between instruments. Generally, the most common sensor type used, the sensitivity and accuracy decrease over time. Infra-red sensors could potentially be less vulnerable to certain environmental factors but may be more costly. While Bailey et al. have clearly illustrated, through their experiments, the performance difference of devices employing different technologies, there is a loss in the sensitivity of electrochemical sensors over their lifetime, which has a negative impact on measurement accuracy [4,5].

Infrared and electrochemical exhaled carbon monoxide meters differ in several technical specifications: the infrared method is very sensitive-in many cases, enabling ppm (parts per million) level measurements-with a response time in milliseconds. However, this usually involves larger instruments and requires regular calibration processes that are rather complex. The response time is generally of the order of seconds with a comparable measurement accuracy and moderate precision from the electrochemical method. In general, electrochemical instruments are smaller and portable, require less regular calibration, and can be easier to use. Each one of these technical features certainly influences the range of applications and user preferences significantly (Table 2) (Figure 4) [2-5,11,12].

Table 2. Comparison of infrared and electrochemical methods for measuring exhaled carbon monoxide

Feature	Infrared (IR)	Electrochemical (EC)
Measurement Sensitivity	High, usually at the ppm level	Medium, usually at the ppm level
Response Time	Usually fast, milliseconds	Usually slower, seconds
Device Size	Often large, difficult to transport	Usually small, portable
Calibration Requirements	Requires regular and complex calibration	Requires less regular and simpler calibration
Possibility of Inaccurate Measurement	It can be affected by environmental conditions (e.g. humidity and temperature changes); the accuracy of the instrument requires regular calibration and maintenance.	Measurement errors can occur due to sensor life and contamination; generally, less affected by environmental conditions.

* Details regarding sample size, study population, and device type corresponding to the studies compared in this table are provided in Table 1.

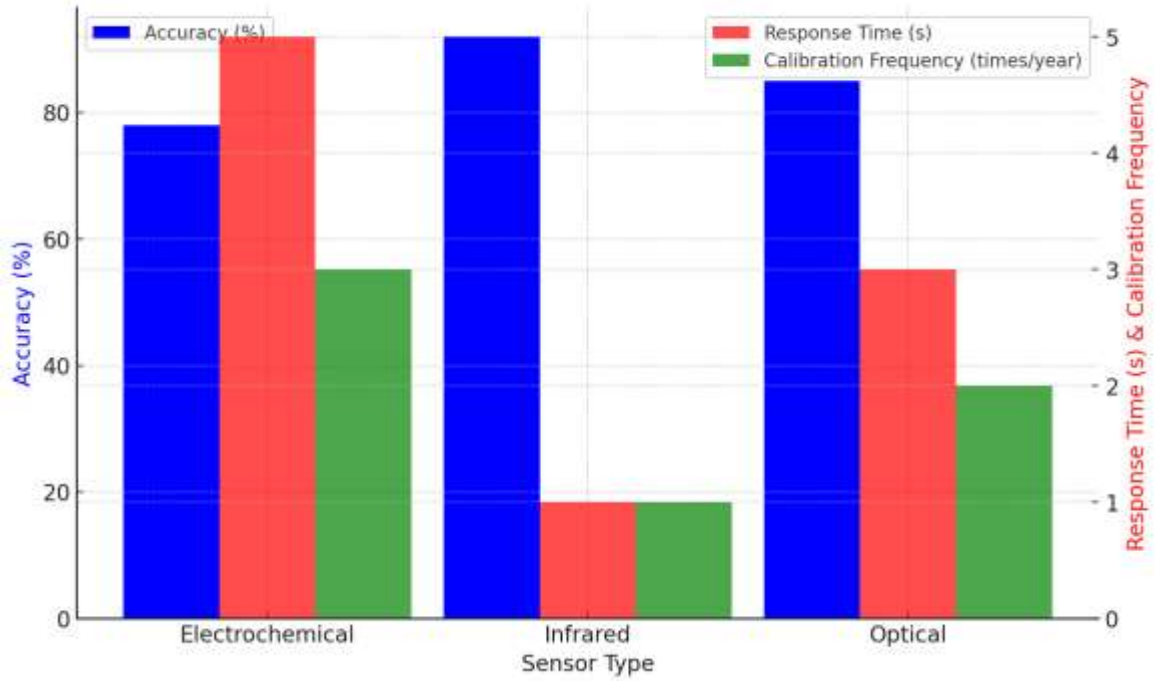


Figure 4. Comparison Of Different Sensor Technologies.

Various technical problems during the measurement of exhaled carbon monoxide with the help of measuring devices can yield incorrect results. A frequent malfunction includes sensor degradation due to time elapsed since, for example, electrochemical and infrared sensors lose their sensitivity with age. Clearly, the regular replacement of sensors or the upgrade to more resistant technologies will do much to alleviate this problem. Moreover, an older edition of firmware or software could also include calculation mistakes; therefore, periodic updating of those with the latest patches is recommended. Other possible problems could be instability in either batteries or power supplies, yielding variable readings, and faulty displays or interfaces could potentially deceive users into interpreting results incorrectly [4-5,11].

Devices are also susceptible to external factors, including electromagnetic interference from other nearby electronics, which can affect sensor performance. Such risks can be minimized by proper shielding and isolation of the device. Besides, defective seals or gaskets may develop air leaks that could interfere with internal pressure and take its toll on the accuracy of sensors. These need to be replaced and inspected routinely to avoid any failure. Finally, blockages in the flow path due to dust, debris, or condensation may interfere with the air reaching the sensor, therefore making the measurement quality poor. Regular maintenance of the device, such as cleaning the device, is very important in the device's proper functioning [4-5,11].

There is no consensus on the appropriate period of smoking abstinence before exhaled CO measurement. Recommendations range from 12 to 24 hours, although some suggest a shorter period such as 20 minutes to 1 hour. This discrepancy in results arises because the period required to be measured would depend on individual metabolism and pattern of smoking, also considering that sometimes the sensitivity of devices may vary. More research needs to be undertaken to make the protocols uniform and enhance test procedures to obtain more clinically valid results [5,11,12].

Ambient Environment

The performance of exhaled CO meters will be influenced directly by the environmental conditions. More precisely, ambient temperature, humidity, and air pressure interfere with correct sensor function. Olson et

al. investigated the effect of environmental conditions on the results of CO measurement and concluded that high humidity had especially affected the accuracy of the devices negatively [4]. It is consequently appropriate to pay attention to the conditions surrounding the devices in use and, if possible, carry out measures in standardized environments. Other environmental factors that may affect the accuracy of CO meters are ambient temperature and moisture. High levels of humidity interfere with the internal mechanisms and give false results from the instrument. On the other hand, intensely hot or cold air can lead to the failure of sensors to respond appropriately. Sensors may also undermeasure carbon monoxide in conditions of high humidity [11,12].

User Errors

Another significant factor contributing to the accuracy of the results by the exhaled CO meters involves user-created errors. Amongst the major reasons behind faulty results is that individuals operating the device do not apply appropriate breathing techniques or are not following instructions for the use of the device. Inadequate breathing leads to the sensors not making correct measurements. Sato et al. demonstrated that users who did not apply correct breathing techniques obtained incorrect results [12]. It is, therefore, of utmost importance that the users are enlightened on the use of the device and taught the proper techniques. Failure to breathe or use the device in line with instructions could also lead to incorrect measurements. Failure to breathe profoundly might result in a situation where the levels of CO measured by the device may be lower than it is. It is, therefore, essential that the users use the device right and conduct the test accordingly [13].

The incorrect measurement of carbon monoxide of smokers is either because of errors in usage or varies according to personal factors. Conditions such as inflammatory processes (respiratory tract infections) could interfere with levels of exhaled CO and further damage the accuracy of measurement. Respiratory tract infection, particularly lower respiratory tract infection, may cause transient inflammation that increases the level of exhaled CO. This may interfere with proper results by combining with CO levels related to smoking[18,19].

During an infection of the respiratory tract, inflammation may lead to epithelium destruction and oxidative stress, which increases CO production. This may complicate the evaluation of smoking in patients due to a transient rise in the exhaled CO level. In a study conducted by Montuschi et al., it was stated that in patients with COPD (Chronic Obstructive Pulmonary Disease), the exhaled CO levels increased, and this is representative of the inflammatory response. The situation becomes more complicated in cases of respiratory tract infections since the increase in CO can be independent of smoking as reflected in measurements[18].

All CO exhaled measurements done in the presence of infection should, therefore, be interpreted with a lot of caution. Particularly in inflammatory diseases and acute respiratory tract infections, the levels of CO in exhaled air may mislead one from the facts. Pellegrino et al. identified infection and inflammation as some of the factors that surround the interpretation of pulmonary function tests. According to them, this increased inflammation due to infection might affect the lung function to cause a deviation from the real value of CO measurements (Figure 4)[19].

Individual factors

Most commonly, smoking is evaluated by measuring exhaled CO. However, the measurements may be misleading in patients with chronic diseases and/or using medications. These are conditions of diseases that chronically affect the lungs-particularly COPD and asthma, which might increase endogenous production of CO and give rise to increases. Indeed, in the study performed by Montuschi et al. COPD patients had higher exhaled CO compared to healthy subjects due to increased production of CO because of inflammation in the airways. Similarly, more severe inflammation in asthma may result in increased levels of exhaled CO. However, metabolic diseases including diabetes mellitus may also affect CO through increased systemic inflammation. Increased inflammation and oxidative stress in uncontrolled diabetic patients may raise CO production and make the exhaled CO measurements misleading. For this reason, health professionals assessing smoking should consider this, based on chronic diseases of patients [18-20].

Besides chronic diseases, some medicines applied can change the level of exhaled CO. Anti-inflammatory medication, like corticosteroids, suppresses inflammation in the airways and hence decreases the levels of exhaled CO. These medications, widely used in diseases such as COPD and asthma, might have a direct influence on measurement results by reducing the inflammation. On the other hand, statins have a systemic inflammation-reducing impact that also decreases the levels of exhaled CO. Such drugs can suppress the inflammatory response and result in lower levels of CO. To interpret correctly the results of exhaled CO measurement, the current pharmaceutical treatment of a person must be paid attention to too. In case these effects of drugs and diseases on CO levels are ignored, a wrong result may be obtained, and the process of evaluating smoking can be misleading. It is in this regard that the characteristics of diseases and drugs in the exhaled CO measurements bear serious importance to be considered while making correct clinical decisions[17-20].

Measurement errors in exhaled carbon monoxide (eCO) assessment have consequences that extend beyond technical issues and may directly influence both clinical practice and public health. Clinically, misclassification of smoking status due to inaccurate CO readings can lead to inappropriate counselling and failure to provide timely cessation interventions, thereby reducing the effectiveness of treatment programs and follow-up care[12,17]. In patients with chronic respiratory conditions, such as COPD or asthma, misleading CO values may obscure disease activity and interfere with therapeutic decision-making [12]. On a broader scale, inaccurate eCO data can distort smoking prevalence estimates, undermine surveillance of tobacco control measures, and misguide allocation of healthcare resources at the population level [18,19]. Therefore, improving the accuracy of CO measurement is essential not only for ensuring reliable patient care but also for safeguarding the validity of public health initiatives targeting tobacco use.

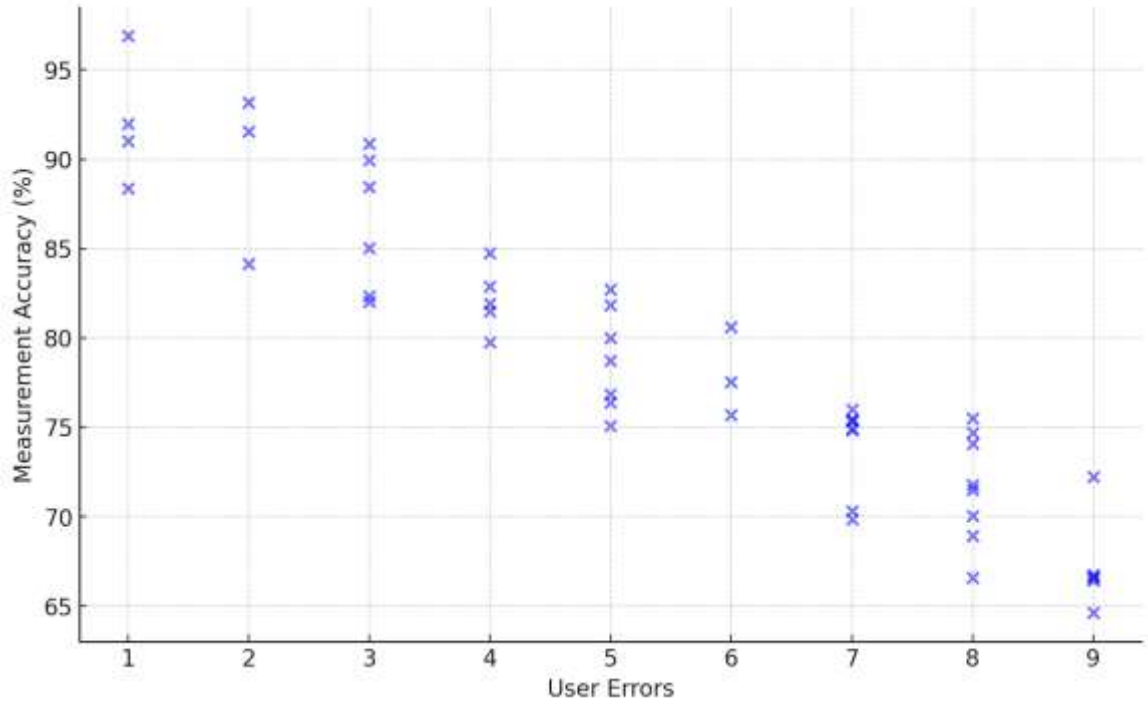


Figure 4. Impact of Environmental Factors on Measurement Error.

Device Age and Technological Innovations

It includes those operating on very outdated technology and the failure to upgrade to new sensor technologies resulting in faulty measurements. It has been observed that older devices remain behind in performance compared to those possessing the latest technological advancements. Wigfield and Hollebone's

studies mentioned that with increased age, the performance of the sensors deteriorates, hence providing an adverse impact on the accuracy of measurement [8]. Regular renewal of the devices by updating them with the latest technologies is thus essential to obtain more reliable results. Generally, sensors lose their accuracy as time passes. Regular checking of the devices and replacing of the sensors should be made when required. Especially in the devices used for a long time, reduced sensitivity of sensors may result in erroneous measurement (Figure 5) [14].

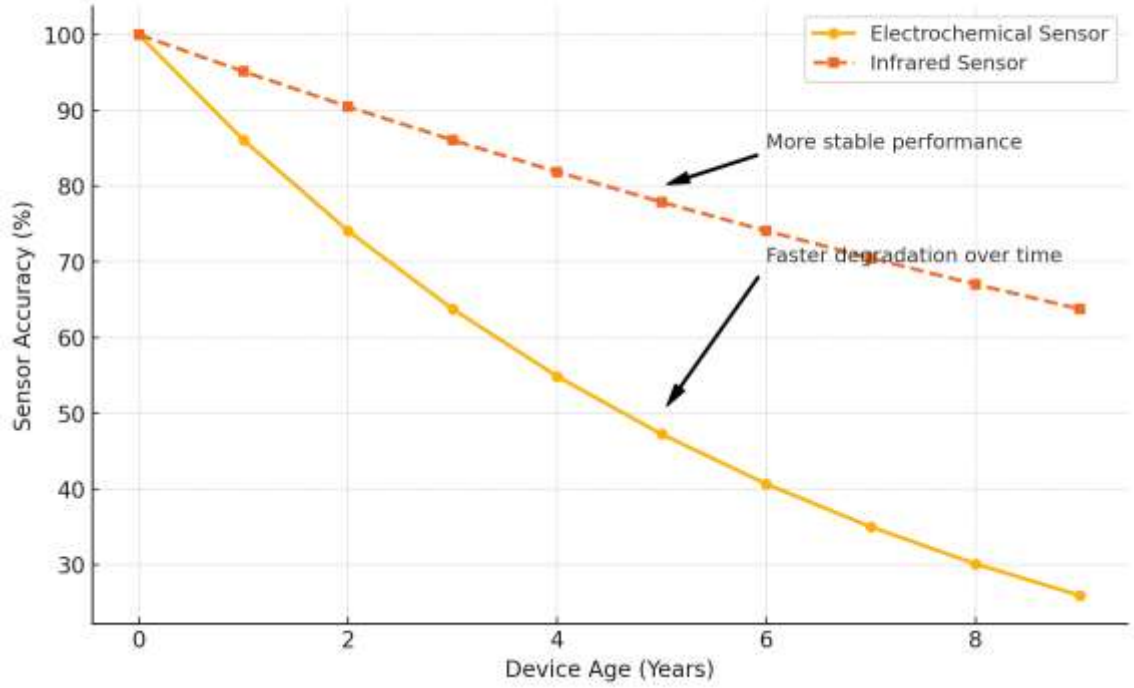


Figure 5. Effect of Device Aging on Sensor Accuracy: Comparison Between Electrochemical and Infrared Sensors.

Conclusion

CO meters play an important role in smoking cessation and in the assessment of acute CO exposure. Usually, the accuracy of a measurement is compromised for several reasons: poorly calibrated devices, outdated sensor technologies, and temperature or humidity environmental influences being only a few. Besides, incorrect breathing by users adds to the inaccuracy of the reading. These, through regular calibration, routine maintenance of devices, and education of users on proper handling, will improve the clinical reliability of the CO meters.

Apparently, in the clinically practical application of exhaled CO measurement assessing smoking status, there is no consensus on what period of abstinence from smoking is advisable before testing. Current recommendations cover very different time periods. This variation owes to individual metabolism, pattern of smoking, and sensitivity of devices which may measure the CO level. Further studies are required to arrive at uniformity in protocols and improvement in testing procedures for more clinically helpful results.

Soon, the development of more advanced CO meters using enhanced sensor technology, which has a much smaller susceptibility to environmental conditions, is likely to result in better diagnostic precision. It would, on the one hand, provide more reliability in the detection of active status, but also acute CO exposure would benefit from it. If this integration into practice by clinicians is done, this would indeed help them to make better judgments for better patient management and sensible smoking cessation programs.

References

1. Ryter SW, Choi AM. Carbon monoxide in exhaled breath testing and therapeutics. J Breath Res. 2013;7:017111.
2. Vreman HJ, Stevenson DK, Oh W, et al. Semiportable electrochemical instrument for determining carbon monoxide in breath. Clin Chem. 1994;40:1927–33.
3. Mahoney JJ, Vreman HJ, Stevenson DK, Van Kessel AL. Measurement of carboxyhemoglobin and total hemoglobin by five specialized spectrophotometers (CO-oximeters) in comparison with reference methods. Clin Chem. 1993;39:1693–700.
4. Bailey SR, Russell EL, Martinez A. Evaluation of the AVOXimeter: precision, long-term stability, linearity, and use without heparin. J Clin Monit. 1997;13:191-8.
5. Olson KN, Hillyer MA, Kloss JS, Geiselhart RJ, Apple FS. Accident or arson: is CO-oximetry reliable for carboxyhemoglobin measurement postmortem? Clin Chem. 2010;56:515–9.
6. PubMed®. National Library of Medicine. The United States National Library of Medicine (NLM). https://pubmed.ncbi.nlm.nih.gov (Accessed: 26 August 2025).
7. Google Scholar. GOOGLE, Alphabet Inc. https://scholar.google.com.tr (Accessed: 26 August 2025).
8. Cochrane Library: Cochrane reviews. Wiley. https://www.cochranelibrary.com.
9. Web of Science™. Clarivate. https://www.webofscience.com/wos/woscc/basic-search (Accessed: 26 August 2025).
10. Researchgate. © 2008-2025 ResearchGate GmbH. https://www.researchgate.net (Accessed: 26 August 2025).
11. Ramieri A Jr, Jatlow P, Seligson D. New method for rapid determination of carboxyhemoglobin by double-wavelength spectrophotometry. Clin Chem. 1974;20:278–81.
12. Sato S, Nishimura K, Koyama H et al. Optimal cutoff level of breath carbon monoxide for assessing smoking status. Chest 2003;124:1749-54.
13. Wigfield DC, Hollebone BR, MacKeen JE, Selwin JC. Assessment of the methods available for the determination of carbon monoxide in blood. J Anal Toxicol. 1981;5:122–5.
14. Widdop B. Analysis of carbon monoxide. Ann Clin Biochem. 2002;39:122–5.
15. Miller MR, Hankinson J, Brusasco V et al. Standardisation of spirometry. Eur Respir J. 2005;26:319-38.
16. Pickering TG, Hall JE, Appel LJ et al. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005;45:142-61.
17. Middleton ET, Morice AH. Breath carbon monoxide as an indication of smoking habit. Chest. 2000;117:758-63.
18. Montuschi P, Kharitonov SA, Barnes PJ. Exhaled carbon monoxide and nitric oxide in COPD. Chest. 2001;120:496-501.
19. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948-68.
20. Högman M, Lafih J, Meriläinen P, Bröms K, Malinovschi A. Janson C. Extended NO analysis in a healthy subgroup of a random sample from a Swedish population. Clinical Physiology and Functional Imaging. 2009;29:18-23.

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Psikiyatrik Boyutlarıyla Dürtüsellik

The Psychiatric Dimensions of Impulsivity

Caner Yeşiloğlu[1], Tunahan Sun[2], Mehmet Emin Demirkol[1], Lut Tamam[1]

[1]Çukurova Üniversitesi Tıp Fakültesi, Ruh Sağlığı ve Hastalıkları Anabilim Dalı, Adana, Türkiye
[2]Düziçi Devlet Hastanesi, Ruh Sağlığı ve Hastalıkları Bölümü, Osmaniye, Türkiye

ABSTRACT
This review explores the multifaceted psychiatric dimensions of impulsivity. Defined by patterns of unplanned, rapid actions, risk-taking, and reward-seeking behavior, impulsivity is a key feature in many psychiatric disorders. Impulsive behavior patterns are observed at a clinical level in approximately 11% of individuals. Impulsivity is seen in more than 70% of attention deficit and hyperactivity disorder (ADHD) cases and significantly affects academic and social functioning in these individuals. Neurobiologically, regions such as the prefrontal and orbitofrontal cortex, along with neurotransmitter systems like serotonin, dopamine, and norepinephrine, play a critical role in impulsive behavior. Gender differences and hormonal influences also shape how impulsivity is expressed. Impulsivity is notably associated with disorders such as ADHD, personality disorders, mood disorders, and substance use disorders. Assessment methods include self-report questionnaires, behavioral laboratory tasks, and biological measurements. In conclusion, impulsivity is a complex and multidimensional behavioral pattern that plays a significant role in understanding psychiatric disorders. Future research in this field is essential to better understand the biological underpinnings of impulsivity and its role in mental illness, which will be crucial for improving therapeutic approaches.
Keywords: Impulsivity, psychiatric disorders, neurobiology, gender differences, substance use disorders, neurodevelopmental disorders

ÖZET
Bu derleme, dürtüsellik kavramının psikiyatrik boyutlarını çok yönlü olarak incelemektedir. Dürtüsellik; plansız ve hızlı hareket etme, risk alma, ödül arayışı gibi davranış örüntüleriyle tanımlanır ve birçok psikiyatrik bozukluğun temel belirtileri arasında yer almaktadır. Bireylerin yaklaşık %11'inde dürtüsel davranış örüntüleri klinik düzeyde gözlenmektedir. Dürtüsellik, dikkat eksikliği ve hiperaktivite bozukluğu (DEHB) olgularının %70'inden fazlasında görülmekte ve bu bireylerde akademik ve sosyal işlevselliği önemli ölçüde etkilemektedir. Nörobiyolojik düzeyde prefrontal ve orbitofrontal korteks gibi beyin bölgeleri ile serotonin, dopamin ve noradrenalin sistemlerinin dürtüsellikte belirleyici olduğu gösterilmiştir. Cinsiyet farklılıkları ve hormonal etkiler dürtüsel davranışların ortaya çıkışında önemli bir role sahiptir. Dürtüsellik; DEHB, kişilik bozuklukları, duygudurum bozuklukları ve madde kullanım bozuklukları gibi birçok psikiyatrik bozuklukta önemli bir belirti olarak ön plana çıkmaktadır. Değerlendirmelerde öz bildirim ölçekleri, davranışsal testler ve biyolojik ölçümler birlikte kullanılmaktadır. Sonuç olarak, dürtüsellik çok boyutlu ve kompleks bir davranış örüntüsü olup, psikiyatrik bozuklukların anlaşılmasında önemli bir yere sahiptir. Bu alanda yapılacak ileri araştırmalar, dürtüselliğin biyolojik temellerinin ve psikiyatrik bozukluklardaki rolünün daha iyi anlaşılmasına katkı sağlayacak, tedavi yaklaşımlarının iyileştirilmesi açısından büyük önem taşıyacaktır.
Anahtar kelimeler: Dürtüsellik, psikiyatrik bozukluklar, nörobiyoloji, cinsiyet farklılıkları, madde kullanım bozuklukları, nörogelişimsel hastalıklar

Giriş

Dürtüsellik, bireyin çevresel koşullara yeterince uyum sağlamadan, düşünmeden hareket etmesiyle karakterize edilen ve sıklıkla istenmeyen sonuçlara yol açan, ani ve çoğu zaman riskli davranışlarda bulunma eğilimi olarak tanımlanmaktadır. Dürtüsellik; dikkatsizlik, sabırsızlık, yenilik arayışı, risk alma, heyecan ve zevk arayışı, zarar görme riskini düşük görme, dışa dönüklük gibi özelliklerle karşımıza çıkar[1]. Psikiyatrik hastalıkların uluslararası kabul görmüş sınıflandırma sistemlerinde doğrudan ifade edilmekte ve dürtüsel

Correspondence Address / Yazışma Adresi
Tunahan Sun, Düziçi Devlet Hastanesi, Ruh Sağlığı ve Hastalıkları Bölümü, Osmaniye, Türkiye e-mail: tunasun01@gmail.com

2025;34(3):195-208
doi:10.17827/aktd.1698682
Geliş tarihi/ Received: 13.05.2025
Kabul tarihi/Accepted: 26.08.2025

davranışlar örneklendirilmektedir[2]. Birçok psikiyatrik bozukluğun temel belirtileri arasında dürtüsellik yer almaktadır. Ancak psikiyatrik bozukluklarda dürtüsellik rolünü araştıran sınırlı sayıda çalışma bulunmaktadır[3].

Dürtüsellik farklı araştırmacılar tarafından farklı şekillerde tanımlanmıştır. Eysenck'e göre dürtüsellik, risk alma, plan yapma eksikliği ve hızlı düşünememe ile ilişkilidir[4]. Patton ve diğerleri ise dürtüsellik kavramını hazırlıksız aniden hareket etme, dikkati odaklayamama ve plan yapmadan, yeterince düşünmeden hareket etme şeklinde üç ayrı boyutta değerlendirmiştir[5]. Deneysel açıdan büyük ve ertelenmiş ödüllere değil, küçük ve doğrudan ödüllere yönelme olarak tanımlanmaktadır[6]. Dürtüsellik yeterince planlanmamış, aşırı riskli ya da duruma uygun olmayan, genellikle olumsuz sonuçlara yol açan davranışlar kümesidir[7]. Dürtüsellik yalnız bir eylem değil bir davranış örüntüsüdür. Sıklıkla sonuçlarını değerlendiremeden yapılan davranışlar olarak görülmektedir[8]. Stahl ise iç veya dış uyaranlar veya tepki eğilimleri tarafından tetiklenen ve uzun vadeli hedeflerle bağdaşmayan spontan davranışlar olarak tanımlamıştır[9]. Dürtüsellik kısaca kendiliğinden ve düşünmeden hareket etme eğilimi olarak tanımlamıştır. Ancak bu durum plan yapamama, azim eksikliği, maceraperestlik, zayıf öz disiplin, yenilik arayışı boyutları olan komplike bir durumdur[10]. Geniş katılımcılı güncel bir çalışmada ise, dürtüselliğin bireyler arasında farklılık gösteren, kalıcı bir kişilik özelliği olabileceği ortaya konmuştur[11].

Dürtüsellik genellikle istenmeyen sonuçlara ve uygunsuz durumlara yol açan, zamanlama açısından ifade edilmiş ve risk taşıyan yaygın bir eylem olarak da tanımlanabilir. Dürtüsel bireyler hem kendileri hem de başkaları için zararlı olabilmektedir. Bu nedenle dürtüsellik; iç ve dış uyaranlara karşı, kendisi ve başkaları için olumsuz sonuçları düşünmeden hızlı ve planlanmamış davranışları şeklinde de tanımlanmıştır[12]. Dürtüsellik, tek bir eylemden ziyade bir davranış örüntüsünü ifade eder. Bilinçli bir şekilde hareketin sonuçlarını düşünme fırsatı vermeden hızlı ve planlanmamış harekettir. Bu özellik, dürtüsellik ile planlayarak gerçekleştirilen kompulsif davranışlar ve bozulmuş yargılama arasında ayırt edicidir[8]. Bu tanımlamalara rağmen, dürtüselliğin hala anlaşılır ve kapsamlı bir açıklaması olmadığı ve normal ile hastalık arasındaki sınırların kesin olmadığı belirtilmelidir.

Bu derlemede, dürtüsellik kavramını psikiyatrik açıdan bütüncül bir perspektifle ele almak, nörobiyolojik temelleri, değerlendirme yöntemleri ve klinik yansımaları ışığında alandaki güncel bilgi birikimini ortaya koymak amaçlanmıştır. Ayrıca dürtüselliğin çeşitli psikiyatrik bozukluklarla nasıl etkileşime girdiği tartışılarak, tanı ve tedavi süreçlerinde dikkate alınması gereken yönlerine vurgu yapılması hedeflenmektedir. Bu sayede, dürtüselliğin psikopatolojiyle ilişkisine dair çok boyutlu bir çerçeve sunulması ve klinik uygulamalara katkı sağlayacak bir literatür temeli oluşturulması amaçlanmaktadır.

Dürtüselliğin Alt Türleri

Motor Dürtüsellik

Motor dürtüsellik, bireyin ani bir şekilde ve önceden düşünmeksizin davranış başlatma eğilimini ifade etmektedir. Genellikle yanıt baskılama mekanizmalarındaki yetersizlik ile ilişkilendirilmekte ve Go/No-Go veya Stop-Signal görevleri ile değerlendirilmektedir[16]. Dikkat eksikliği ve hiperaktivite bozukluğu (DEHB), borderline kişilik bozukluğu (BKB) ve madde kullanım bozukluklarında yaygın olarak gözlemlenmektedir[8].

Bilişsel Dürtüsellik

Bilişsel dürtüsellik, düşünce süreçlerindeki acelecilik, dikkat eksikliği ve planlamada güçlük ile karakterizedir. Bu alt tür, bireyin karar verirken olasılıkları yeterince değerlendirememesi ve sonuçları öngörmeden hızlı çıkarımlarda bulunmasıyla kendini göstermektedir. Özellikle ergenlerde ve manik dönemlerde sık görülür[5].

Emosyonel Dürtüsellik

Emosyonel dürtüsellik, bireyin duygusal uyarılara karşı aşırı ve kontrolsüz tepkiler vermesi ile tanımlanır. Bu durum ani öfke patlamaları, duygu regülasyonunda bozulma ve çatışma davranışları şeklinde ortaya çıkabilir[12]. BKB, travma sonrası stres bozukluğu ve bazı affektif bozukluklarda ön plandadır[5,8].

Nörobiyolojik Açıdan Dürtüsellik

Dürtüsel saldırganlık sergileyen bireylerin benzer eylemleri göstermeyenlere göre daha büyük uyarılmış beyin potansiyel amplitüdleri olduğu ve beyin omurilik sıvısında serotonin metabolit seviyelerinin daha yüksek olduğu gösterilmiştir[13,14]. Agresyon gösteren dürtüsel bireyler ile tasarlanmış davranan bireylerin ilaçla tedaviye yanıtları farklı olduğu aynı zamanda elektroensefelogram dalgalarının da anlamlı farklılığı olduğu saptanmıştır[15,13] .

Karar verme, yanıt seçme, davranışsal baskılama süreçlerinde prefrontal korteks (PFK) ve orbitofrontal korteks (OFK) önemli rol almaktadır. OFK, kişinin eylemlerinin sonuçlarıyla ilgili mevcut bilgilere dayanarak davranışı yönlendirmede öne çıkmaktadır. Frontal lob hasarı olan bireylerde dürtüselliğin görülmesi bunu desteklemektedir. Karar verme, planlama ve tepki verme süreçleri frontal korteks tarafından yönetilmektedir. Uyarana tepkinin belirlenmesinde başlıca rolü OFK almaktadır. Çalışmalar, ventromedial PFK ve OFK gibi bölgelerin dürtüsel davranışları düzenlemede merkezi rol oynadığını göstermiştir[16]. Striatum gibi ödül sistemi ile ilişkili bölgelerle, PFK gibi bilişsel kontrol sistemleriyle ilişkili bölgeleri birleştiren kortiko-striatal devreler dürtüsellikte önemli bir rol oynamaktadır[16,17]. Hüpen ve ark. dinlenme hâlinde beyin bağlantılarını incelediği bir çalışmada, dürtüsellikle ilişkili ağın serebellum, beyin sapı ve temporal lob gibi bölgeleri de içerdiğini ortaya konulmuştur[17].

Serotonin, nöradrenalin, dopamin, glutamat ve GABA dürtüsellik üzerinde etkili olan temel nörotransmiterlerdir (NT). Bu NT'ler arasında serotonin ve dopamin ön plana çıkmaktadır. Serotonin seviyelerindeki azalmanın davranışın baskılanmasını azalttığı belirtilmiştir[18]. Beyinde serotonin düzeyinin azalması ile davranışların baskılanması güçleşmektedir. Serotonin düzeylerinin azalması dürtüselliği arttırırken, dopamin ve serotonin dengesizliği orbito-ventromedial kortekste işlevsel bozukluklara neden olabilmektedir[16]. İntihar eden bireylerde ve şiddet suçlularında serotonin metabolitlerinin azaldığı görülmüştür[19–21]. Serotonin eksikliği özellikle intihar düşüncesi ve saldırganlık gibi dürtüsel davranışlar ile ilişkilendirilmektedir[22]. Raji ve ark. düşük serotonerjik iletimin orbito-ventromediyal PFK'de dopaminerjik düzensizliğe yol açarak agresif davranışları ve dürtüselliği artırdığını bildirmiştir[16]. Ancak DEHB tanılı hastalarda metilfenidat gibi psikostimulanlar dürtüsellik üzerine daha etkili olmuştur[23]. Noradrenalin sistemi, özellikle dürtü kontrolünde önemli bir role sahiptir[24,25]. Atomoksetin ve modafinil de noradrenerjik veya dopaminerjik iletim üzerinde etkili olmuştur[26,27]. Tüm bunlar çerçevesinde serotoninin yanıt inhibisyonunda sınırlı bir rol oynadığı ve diğer nörokimyasal sistemlerin de yanıt inhibisyonunu düzenlemede etkili bir rolü olduğu düşünülebilir.

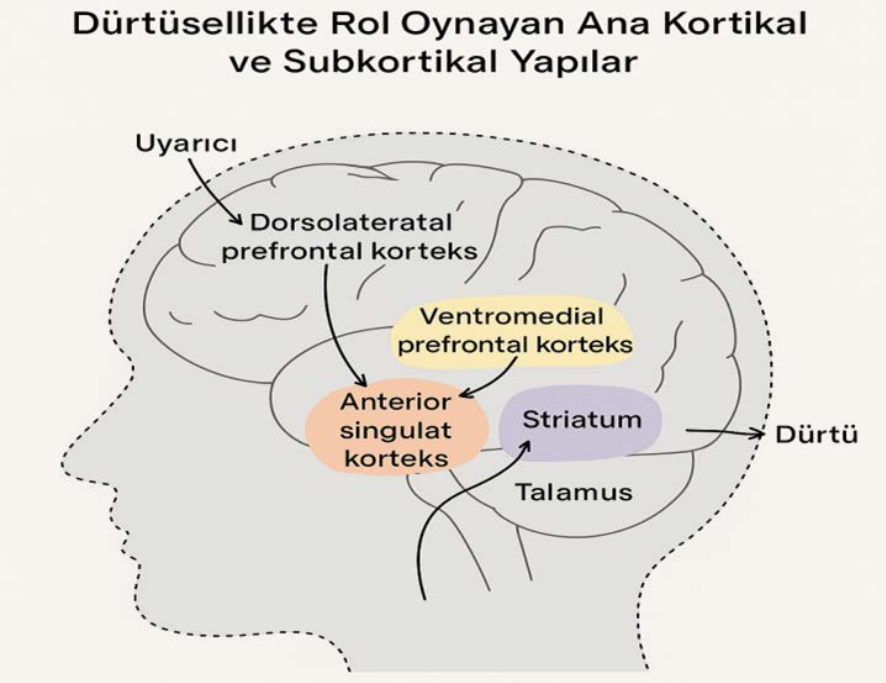
Stres hormonları ve diğer biyokimyasal faktörlerde nörobiyolojik açıdan dikkat çekmektedir. Örneğin artmış kortizol ve adrenalin düzeyleri dürtüsellik ile ilişkilendirilmiştir[16]. Ergenlik döneminde ise beyin yapısındaki değişiklikler etkili olmaktadır. Azalmış gri madde hacmi ve beyaz cevher bütünlüğü, artmış dürtüsellikle ilişkili bulunmuştur[28]. Bu bulgular ışığında dürtüselliğin birçok nörobiyolojik mekanizmayla ilişkili olduğu düşünülebilir.

Stres yanıtı, organizmanın çevresel tehditlere verdiği evrimsel olarak şekillenmiş bir adaptif mekanizmadır. Bu süreçte hipotalamo-hipofiz-adrenal (HPA) aksı temel rol oynar. Stres algılandığında hipotalamustan kortikotropin salgılatıcı hormon salınır; bu da hipofiz bezinden adrenokortikotropik hormonun salgılanmasını uyarır ve nihayetinde adrenal korteksten kortizol salınır. Kortizol, enerji mobilizasyonunu artırarak kısa vadede organizmanın stres etkeniyle başa çıkmasını sağlar. Ancak kronik stres, HPA aksının sürekli uyarılmasıyla nörobiyolojik yapılar üzerinde olumsuz etkiler oluşturabilir; özellikle de prefrontal korteks, amigdala ve hipokampus gibi dürtü kontrolünde kritik rol oynayan beyin bölgelerinde görülmektedir[16].

Yüksek kortizol düzeyleri, prefrontal korteksin inhibisyon işlevini baskılayabilirken, amigdaladaki reaktiviteyi artırarak duygusal yanıtların regülasyonunu bozar. Bu da bireylerde dürtüsel karar verme, ani öfke patlamaları ve riskli davranışlara eğilimi artırabilir. Hüpen ve arkadaşlarının çalışmasında dürtüsellik ile ilişkili fonksiyonel beyin ağlarının HPA aksı aktivasyonu ile doğrudan etkileşim içinde olduğu bildirilmiştir[17]. Ayrıca Green ve arkadaşları, ergenlik döneminde HPA aksı aktivitesinin artmasının, gri madde hacminde azalma ve beyaz cevher bütünlüğünde bozulma ile ilişkili olduğunu ve bu yapısal değişikliklerin dürtüsellikle bağlantılı olduğunu ortaya koymuştur[28].

Özetle, stres yanıtının biyolojik aracısı olan HPA aksı, dürtü kontrolünü yöneten kortikal ve limbik yapılarda işlevsel değişiklikler oluşturarak dürtüsellik düzeylerini etkileyebilir. Bu etkileşim, özellikle travma öyküsü olan bireylerde, sınırda kişilik bozukluğu, DEHB ve madde kullanım bozukluğu (MKB) gibi psikiyatrik hastalıklarda daha belirgin olabilir.

Dürtüsellikte rol oynayan ana kortikal ve subkortikal yapılar Şekil 1'de gösterilmektedir.



Şekil 1. Dürtüsellikte Rol Oynayan Ana Kortikal ve Subkortikal Yapılar.

Dürtüsellik ve Tepki Bastırmada Bozulma

Dürtüselliğin çoğunlukla frontostriatal devrelerdeki inhibisyon bozukluğuna bağlı olarak ortaya çıktığı ve bu nedenle bireylerin davranışlarını planlı biçimde bastırmakta güçlük yaşadığı vurgulanmıştır[16]. Bu tür inhibisyon kusurlarını ölçmek için Stop-Sinyal ve Go/No-Go gibi laboratuvar görevleri sıkça kullanılmaktadır[16]. Dürtü kontrolünde bozulma, DEHB, Obsesif Kompulsif Bozukluk (OKB) ve başka hastalıklarda ortak görülür.

Nöropsikiyatrik hastalıklardaki tepki bastırma sorunlarıyla ilişkili nöropsikiyatrik durumlarda yanıt inhibisyonu işlevi yetersizdir. DEHB, birçok kişi tarafından dürtüsellikle ilişkili bir bozukluk olarak kabul edilir. DEHB tanılılarda çocuk yaşta ve yetişkinlikte dürtüsel eylemler farklılık gösterse de belirtiler devam etmektedir. DEHB tanılı çocuklarda ve yetişkinlerde olan tepki bastırma-yanıt inhibisyonu yaşam boyu süren nöropsikolojik bulgulardan biridir[33,34].

OKB hastalarında inhibitör kontrol eksiklikleri fronto-striatal devrelerin işlevselliğine yansımaktadır[35]. Uhre ve ark. yaptıkları güncel bir meta-analizde, OKB hastalarında inhibisyon görevleri esnasında, fonksiyonel manyetik rezonans görüntülemede (fMRI) fronto-striatal bölgelerde anormal aktivasyonlar olduğu bildirilmiştir[35]. Trikotillomani, tekrarlayan bir şekilde saç yolma ve bunun sonucunda rahatsız edici ve fark edilebilir saç kaybı ile görülen bir hastalıktır[2]. Chamberlain ve ark. trikotillomani hastalarında yanıt inhibisyonunda bozulma bildirmişlerdir ve bu bozulmanın büyüklüğü, saç çekme şiddetine ilişkin öznel değerlendirmelerle ilişkilidir[36]. Penades ve meslektaşları OKB hastaları için benzer bozulmaları belirtmiştir[37].

MKB belirtileri arasında kendini tehlikeye atma, tekrarlayan hukuki sorunlar ve kötüleşen davranışlara rağmen madde kullanımının devam etmesi bulunur. Monterosso ve meslektaşları kronik metamfetamin kullanıcılarında kontrol grubuna kıyasla yanıt inhibisyonu eksiklikleri tespit etmiştir[38]. Bu eksikliklerin madde

kötüye kullanımdan önce mi ortaya çıktığını yoksa kimyasal kötüye kullanımın kortikosubkortikal devreler üzerindeki zararlı etkisi sonucunda mı ortaya çıktığı belirlenememiştir.

Cinsiyet ve Dürtüsellik

Cinsiyetler arasında, dürtüsellikte farklılıklar bildirilmiştir. Yapılan çalışmalarda erkeklerde somut ödüller karşısında kadınlarda ise hayali/varsayımsal ödüller karşılığında daha yüksek dürtüsellik eğilimi olduğu gösterilmiştir[16]. Erkeklerde testosteron seviyesi ile frontostriatal bağlantı bütünlüğü arasında pozitif bir ilişki saptanmış, bu durumun erkeklerde somut ödüllere yönelik dürtüselliği arttırabileceği öne sürülmüştür[16]. Erkekler kadınlardan daha sık dürtüsel davranışlarda bulunmaktadır[29,30]. Erkeklerin araçla kaza yapma, düşme, boğulma, elektrik çarpması, ateşli silah kazaları ve yangınlar nedeniyle ölüm oranları kadınlardan önemli ölçüde yüksektir. Adli olaylar, öfke kontrol sorunları, davranım bozuklukları yine erkeklerde kadınlardan daha yüksektir ve dürtüsellik bu durumlar için bağımsız bir risk faktörü olarak saptanmıştır. Ödül ve motivasyon alanında rol alan dopaminerjik sistemin erkeklerde daha reaktif olması cinsiyetler arası farkı açıklayan neden olarak öne sürülmektedir[30].

Cinsiyetler arası dürtüsellik farkının evrimsel teorisine göre erkekler üreme başarısını arttırmak için erkekler arasında hakimiyet kurmaya isteklidir. Rekabete neden olan bu durum dürtüsel saldırganlık ve artan suç oranları ile ilişkilidir[30]. Ayrıca testosteron seviyeleri heyecan arayışı, kısa vadeli hedeflere eğilim, dürtüsellik, baskınlık, rekabetçi tutum ve cinsel uyarılma ile ilişkilidir. Wilson ve Daly tarafından ise erkeklerin daha sık riskli karar alması, kumar oynaması, tehlikeli araba kullanması ve uyuşturucu kullanmasının, riskten daha fazla zevk almaları ile ortaya çıktığı öne sürülmüştür[31]. Bu teoriler erkeklerin dürtüsellik ölçümlerinde heyecan arayışı ve risk alma değerlerinin yüksek olması ile örtüşmektedir. Kadınların üreme başarısı, yaşamı devam ettirmeye bağlıdır. Bu durum bebeklerin anneye daha fazla bağımlı olmasından, kadının yaşamı boyunca taşıyabileceği sınırlı sayıda bebek olmasından kaynaklanmaktadır. Bu nedenle, kadınlar erkeklere göre dürtüsel davranışlara ve tehlikelere karşı daha duyarlıdır ve daha fazla kaçınmaktadır[30].

Öte yandan deney hayvanlarında dişi bireyler, erkeklere göre motor dürtüsellik testlerinde daha yüksek skorlar almıştır. Hayvan çalışmalarında ve bazı insan örneklemlerinde kadınlarda erkeklere göre daha yüksek motor dürtüsellik skorları elde edilmesi, cinsiyete özgü dürtüsellik örüntülerine ilişkin klasik beklentilere ters düşmektedir[32]. Bu durum, özellikle östrojen ve progesteron düzeylerindeki fizyolojik dalgalanmaların, dürtüsellik üzerindeki etkilerinin evrensel ve sabit olmadığını göstermektedir. Östrojenin dopaminerjik sistem üzerindeki iki yönlü etkisi, bu çelişkinin temel nedenlerinden biri olabilir: bazı durumlarda dopamin salınımını artırarak ödül arayışını güçlendirirken, diğer durumlarda reseptör duyarlılığını azaltarak inhibisyon mekanizmalarını zayıflatabilir[16].

Özellikle menstrüel döngünün foliküler fazında, kadınlarda artmış yanıt başlatma eğilimi (motor dürtüsellik) gözlemlenmiştir. Bu fizyolojik durum, davranışsal olarak tepkiselliğin artmasıyla sonuçlanabilir[28]. Buna karşın, luteal fazdaki yüksek progesteron düzeylerinin davranışsal inhibisyonu artırdığı ve dürtüselliği baskıladığı öne sürülmektedir. Bu döngüsel değişim, bazı bireylerde dürtüsellik düzeyinde gözlenen dalgalanmalara ve farklı çalışmalarda elde edilen sonuçlar arasındaki tutarsızlıklara yol açabilir. Ayrıca, bilişsel kontrol ağlarının (prefrontal korteks, singulat korteks) işlevselliğinde kadınların daha fazla durumsal değişkenliğe sahip olduğu, bu nedenle motor dürtüsellik testlerindeki performansın daha büyük birey-içi varyans gösterdiği bildirilmiştir[17]. Dolayısıyla, cinsiyet farklılıkları yalnızca sabit biyolojik farklılıklarla değil, hormonal çevrim, nöroplastisite ve bilişsel yük gibi dinamik faktörlerle de şekillenmektedir. Cinsiyete özgü farklılıkların östrojen ve progesteron düzeylerindeki dalgalanmalara bağlı olduğu düşünülmektedir[32]. Örneğin kadınlarda yüksek östrojen düzeylerinin dürtüsellikte artışla ilişkili olduğu, kadın üreme döngüsünün bazı dönemlerinde kadınların dürtüsel risk alma eğilimlerinin değişkenlik gösterdiği bildirilmiştir[16]. Bu veriler, erkeklerde görülen risk alma eğilimi ve kadınlarda hormonal döngülere bağlı dürtüsel değişkenlik gibi pratik davranış farklılıklarının cinsiyete özgü nörobiyolojik ve evrimsel temelleri olduğunu göstermektedir.

Hormonal Döngü ve Dürtüsellik

Kadınlarda hormon düzeylerindeki dönemsel dalgalanmalar, özellikle menstrüel döngü evrelerine bağlı olarak dürtüsellikte belirgin değişkenliklere yol açabilmektedir. Menstrüel döngü tipik olarak dört faza ayrılır:

menstruasyon, foliküler faz, ovulasyon ve luteal faz. Bu evrelerdeki hormonal dalgalanmalar, özellikle östrojen ve progesteron düzeylerindeki değişimlere bağlı olarak bilişsel kontrol, duygusal regülasyon ve yanıt inhibisyonunu etkileyebilir[16].

Foliküler fazda, östrojen düzeyi artar ve bu dönemde dopaminerjik sistem aktivitesi de artış gösterir. Bu artış, ödül duyarlılığını ve yaklaşım davranışlarını güçlendirerek motor dürtüselliği tetikleyebilir[28]. Ayrıca prefrontal kortekste artan dopamin düzeyi, karar alma süreçlerinde daha hızlı ama potansiyel olarak daha az kontrollü yanıtların verilmesine neden olabilir[32]. Ovulasyon döneminde, östrojen pik yapar ve bu fazda dürtüsellik artışı bazı çalışmalarda belirginleşmiştir, özellikle riskli karar verme ve ani davranış başlatma eğilimlerinde artış gözlenmiştir[17].

Buna karşılık, luteal fazda, progesteron düzeyinin yükselmesiyle birlikte davranışsal inhibisyonun arttığı, yani dürtüsel davranışların azaldığı bildirilmiştir. Progesteronun GABA-A reseptörleri üzerindeki etkileriyle anksiyolitik ve inhibitif yanıtların kolaylaştığı, bu nedenle bu dönemde kadınların yanıt bastırma becerilerinin daha güçlü olduğu öne sürülmektedir[16]. Ancak luteal fazda görülen duygusal değişkenlikler (örneğin sinirlilik, duygudurum dalgalanmaları), bazı bireylerde dürtüsel emosyonel tepkileri artırabilir ve bu da klinik yansımaları daha karmaşık hale getirir[28].

Bu nöroendokrin değişikliklerin bireyler arasında farklı düzeylerde gözlemlenmesi, kadın örneklemlerinde dürtüsellik üzerine yapılan çalışmalarda yüksek birey-içi varyans oluşmasına ve bulgular arasında tutarsızlıklara neden olabilmektedir. Dolayısıyla, hormonal döngü faktörü dikkate alınmadan yapılan dürtüsellik değerlendirmeleri, sonuçların geçerliliğini sınırlayabilir. Klinik çalışmalarda kadın katılımcıların değerlendirilmesinde menstrüel döngü evresinin kontrol değişkeni olarak hesaba katılması, dürtüsellik çalışmalarında metodolojik olarak büyük önem taşımaktadır[17].

Dürtüsellik Ölçümleri Değerlendirmeleri

Dürtüsellik değerlendirmesi çok boyutludur. Dürtüsellik sıklıkla öz bildirim değerlendirmeleri, davranış laboratuvarı değerlendirmeleri ve olaya ilişkin potansiyellerin değerlendirmeleri ile ölçülmektedir. Geleneksel olarak Barratt Dürtüsellik Ölçeği (BIS-11) gibi öz bildirim ölçekleri kullanılmıştır. Ancak modern çalışmalarda biyolojik ölçümler de önem arz etmektedir.

Öz Bildirim Ölçekleri

BIS-11[5] ve Eysenck Dürtüsellik Anketi[39] gibi öz bildirim ölçekleri, dürtüsel davranışların olup olmadığını ve bu davranışların uzun vadeli kalıplar oluşturup oluşturmadığını değerlendirmektedir. Öz bildirim ölçeklerinde kullanılan bazı örnekler şunlardır: "Dürtüsel davranırım" ve "Görevleri dikkatlice planlarım". Öz bildirim ölçeklerinin dezavantajları, anketi dolduran bireyin doğruluğuna güvenmek zorunda olunmasıdır. Ayrıca, bu ölçekler tekrarlanan kullanıma uygun olmadığından, tedavi çalışmalarında kullanımları sınırlıdır.

Davranış Laboratuvarı Değerlendirmeleri

Davranışsal değerlendirme araçları dürtüselliğin motor ve bilişsel bileşenlerini daha nesnel biçimde ölçmeyi hedefler. Go/No-Go ve Stop-Signal görevleri, özellikle yanıt baskılama becerilerini değerlendirmek için kullanılmaktadır[16]. Stop-Signal görevi, bireyin başlatılmış bir davranışı ne ölçüde durdurabildiğini test ederek inhibisyon kontrolünü ölçerken; Go/No-Go görevi uygun ve uygunsuz tepkileri ayırt edebilme yetisini yansıtır[16]. Diğer taraftan, ödül-gecikme tercih görevleri (Delay Discounting Task), bireylerin kısa vadeli ödüller karşısında sabır gösterme kapasitelerini ölçerek, karar verme süreçlerindeki dürtüselliği ortaya koyar[6].

Bu görevler tekrarlanabilirlik ve nesnellik açısından değerlidir. Ancak laboratuvar ortamının doğallıktan uzak olması ve sosyal bağlamı içermemesi nedeniyle ekolojik geçerlikleri sınırlı kalabilmektedir[43,44].

Olaya İlişkin Beyin Potansiyelleri

Dürtüselliğin beyin düzeyindeki yansımaları, özellikle olaya ilişkin beyin potansiyelleri (ERP) gibi elektrofizyolojik yöntemlerle değerlendirilmiştir. Bu ölçümlerde sıklıkla analiz edilen P300 bileşeni, dikkat, karar verme ve inhibisyon süreçleriyle ilişkilidir. Moeller ve arkadaşları (2001), dürtüsel bireylerde P300

amplitüdünün azaldığını ve bu bulgunun dürtü kontrol bozukluklarıyla ilişkili olabileceğini göstermiştir[8]. Ancak bu biyobelirteçler dürtüselliğe özgü değildir; benzer değişiklikler diğer nöropsikiyatrik durumlarda da gözlenmektedir.

Ölçme Araçlarının Sınırlılıkları

Dürtüselliği değerlendirmede kullanılan ölçme araçları her biri kendi içinde değerli bilgiler sunsa da, belirgin sınırlılıklar barındırmaktadır. Öz bildirim ölçekleri, bireyin kendi davranışları hakkındaki subjektif değerlendirmesine dayanır; bu da sosyal istenirlik yanlılığı, içgörü eksikliği veya durumluk değişkenlerin yanıtları etkilemesi gibi faktörlerle geçerliliği sınırlayabilir[5]. Ayrıca bu tür ölçeklerin tedaviye duyarlılığı düşük, tekrarlanan ölçümlerde stabilite sorunları doğurabileceği bilinmektedir[39].

Davranışsal görevler (örneğin Go/No-Go, Stop-Signal), dürtü kontrolünü nesnel biçimde değerlendirse de, ekolojik geçerliliği düşüktür; çünkü bireylerin günlük yaşamlarındaki dürtüsel davranışları tam olarak yansıtmaz[43]. Ayrıca test ortamında verilen motivasyon, dikkat düzeyi ve anlık duygusal durum gibi faktörler performansı etkileyebilir, bu da sonuçların genellenebilirliğini sınırlamaktadır[44].

Biyolojik ölçümler (örneğin ERP bileşenleri, fMRI bağlantıları) dürtüselliğin nöral temelini anlamada ileri teknikler sunsa da, yüksek maliyet, teknik uzmanlık gerekliliği ve yorumlayıcı öznellik gibi faktörlerle klinik pratikte sınırlı kullanılabilirliğe sahiptir[45]. Ayrıca bu ölçümler genellikle dürtüselliğe özgü değildir; dikkat, emosyonel regülasyon veya başka bilişsel süreçlerle de ilişkili olabilir[8].

Tüm bu nedenlerle, tek bir ölçüm aracı ile dürtüselliği eksiksiz şekilde değerlendirmek mümkün değildir. Çok boyutlu, çok yöntemli yaklaşımlar, bu sınırlılıkların etkisini azaltarak daha güvenilir ve bütüncül değerlendirmelere olanak sağlayabilir[45].

Çok Boyutlu Yaklaşımlar

Lamichhane ve ark. davranışsal testler, kalp hızı değişkenliği ve fMRI bağlantı ölçümlerini bir arada kullanarak yaptıkları çalışmada, özellikle duygudurum bozukluğu tanılı hastalarda dürtüsellik boyutlarını %73 oranında açıklayan çoklu modlu modeller geliştirmiştir[45]. Bu tür çok boyutlu yaklaşımlar, dürtüselliği tek bir ölçekten ziyade çok boyutlu olarak değerlendirme imkânı sağlamaktadır[45].

Genel olarak dürtüsellik ölçümlerinin, öz bildirim ölçekleri ile laboratuvar görevleri ve/veya biyolojik ölçümlerin kombine edilerek daha güvenilir hale getirileceği düşünülebilir.

Dürtüsellik ve Psikiyatrik Hastalıkların Sınıflama Sistemlerindeki Yeri

Dürtüsel davranışlar birçok psikiyatrik hastalıkta baskılama mekanizmasının zayıflaması ile ortaya çıkmaktadır. Tek başına tanı koydurucu bir durum olmamakla birlikte klinik duruma eşlik eden semptomlara göre tanı belirlenmektedir. Bipolar duygulanım bozukluğu, B kümesi kişilik bozuklukları, DEHB, OKB, posttravmatik stres bozukluğu, MKB ve dürtü kontrol bozuklukları dürtüselliğin görüldüğü başlıca psikiyatrik hastalıklardır[46].

Dürtü kontrol sorunları, bir kişinin kendisine veya başkalarına zarar verebilecek eylemlere karşı koyma istek ve arzularına tekrar tekrar direnememe durumuyla ilişkilidir. Yıkıcı davranış bozuklukları ise agresyon ve kurallara karşı gelme gibi davranış sorunlarıyla belirginleşir. Her iki durum da Amerikan Psikiyatri Birliği'nin sınıflandırma sistemlerinde önemli değişikliklere uğramıştır. DSM-IV'te "başka bir yerde sınıflandırılmamış dürtü kontrol bozuklukları" başlığı altında sınıflandırılan kleptomani, aralıklı patlayıcı bozukluk, patolojik kumar oynama, piromani ve trikotillomani gibi hastalıklar, karşı konulamayan eylem öncesinde artan bir gerginlik ve uyarılma hissinin oluşumu ve eylem sırasında haz, tatmin ve rahatlama sağlayan durumlar olarak tanımlanmıştır. Davranış bozukluğu ise çocukluk ve ergenlik dönemlerinde başlayan davranış sorunları, öfke sorunları, kurallara uymama, yetişkinlerle sık tartışmalara girme gibi durumlar olarak ifade edilmiştir. DSM-IV'te "genellikle bebeklik, çocukluk veya ergenlik dönemlerinde tanı konan bozukluklar" ve "dikkat eksikliği ve yıkıcı davranış bozuklukları" olarak sınıflandırılan hastalıklar DSM-5'te "yıkıcı bozukluklar, dürtü kontrol ve davranış bozuklukları" başlığı altında birleştirildi. Trikotillomani "obsesif kompulsif spektrum bozuklukları" başlığı altına; patolojik kumar oynama "madde ilişkili bozukluklar ve bağımlılık bozuklukları" başlığı altına; DEHB ise "nörogelişimsel bozukluklar" başlığı altında tanımlandı. Yine DSM-IV'te kişilik

bozuklukları içinde yer alan antisosyal kişilik bozukluğu (ASKB), DSM-5'te "yıkıcı bozukluklar, dürtü kontrol ve davranış bozuklukları" kategorisinde ismen yer aldı ancak tanı ölçütleri hala "kişilik bozuklukları" altında devam etmektedir[47].

Güncel yaklaşımlar ise dürtüselliği boyutsal bir özellik olarak vurgulamaktadır. Yapılan geniş ölçekli bir çalışmada Huang ve ark. dürtüselliği bireyler arasında tutarlı bir farklılık olarak tanımlamış, bu faktörün dürtüsel davranışları öngörmede belirgin olduğunu göstermiştir[11]. Cuthbert ve Insel de dürtüselliği ödül işleme, karar verme gibi nörobiyolojik düzeyde temel süreçler bağlamında inceleyerek kategorik bakış açısının ötesine geçirmeyi önermektedir[48].

Psikiyatrik Hastalıklar ve Dürtüsellik

Psikiyatri rutinin de sık kullanılan BIS-11'in analizinde daha fazla motor aktivasyon, daha az dikkat ve azalan planlama faktörleri ölçeğin belirleyici unsurları olarak saptanmıştır[5]. Psikiyatrik hastalığı olmayan bireylerde de dürtüsellik gözlenebilmektedir. Kişilik bozuklukları, manik epizodlar ve madde kullanım bozuklukları, dürtüselliğin özellikle sık ve yoğun biçimde gözlendiği başlıca psikiyatrik tanılar arasındadır. Bu bozukluklarla dürtüsellik arasındaki ilişki, bu bozuklukların tümünde davranışsal engelleme eksikliği olması nedeniyle tamamen ya da kısmen ortaya çıkar[49,50]. Frontal lob hasarında kişilik bozukluğu belirtileri, dikkat ve planlamada bozulma görülmektedir[51,8]. Manik atak döneminde dürtüsellik ile örtüşen motor aktivasyonda artma ve planlamadan davranışlarda bulunma görülmektedir. Dürtüsellik tek başına tanı koydurmamakla birlikte eşlik eden diğer bulguları da değerlendirerek psikiyatrik tanı belirlenmektedir[52]. Dürtüsellik, bu hastalarda yalnızca tanısal bir özellik değil; aynı zamanda erken nüks, düşük tedavi süresi tamamlama oranı ve tekrarlayan kriz başvuruları ile de ilişkilidir[43].

Antisosyal Kişilik Bozukluğu

ASKB, dürtüsel ve dürtüsel olmayan toplum normallerine aykırı davranışların belirgin görüldüğü psikiyatrik bir tanıdır. ASKB'de dürtüsel saldırganlık ve yasa dışı davranışlar öne çıkar[53].

ASKB tanılı bireylerde beyindeki düşük serotonin düzeyleri ve orbito-frontal korteks bozukluklarının, dürtüsel saldırganlıkla ilişkili olduğu bildirilmektedir[53]. Beyindeki serotonin eksikliğinin orbito-ventromedial kortekste dopaminerjik düzensizliğe neden olduğu ve bunun ASKB'deki dürtüsel agresyonu artırdığı bildirilmiştir[16]. Linnoila ve ark. ASKB tanılı 36 kişiyi değerlendirmiş, dürtüsel şiddet eylemi olan bireylerin beyin omurilik sıvısında serotonin metaboliti 5-hidroksiindol asetik asit düzeylerinin, planlanmış şiddet eylemi olan bireylerden daha düşük olduğunu belirtmiştir[20]. Bu bulgular, ASKB'de tedavi stratejileri geliştirirken serotonerjik yolakların hedeflenebileceğini göstermektedir.

Barrat ve ark. ASKB tanı ölçütlerini karşılayan hükümlü bireylerde saldırganlığı değerlendirmiştir[54]. ASKB tanı kriterlerini karşılayan hükümlüler arasında saldırganlık düşünce ve davranışlarını değerlendirmiştir. Klinik görüşme ile hükümlüleri, dürtüsel saldırgan eylemlerde bulunanlar ve planlanmış saldırgan eylemlerde bulunanlar olarak iki gruba ayırmıştır. 132 hükümlüden, 27'si (%20) öncelikle dürtüsel saldırgan eylemler işlemişken, 30'u (%23) dürtüsel olmayan saldırgan eylemler işlemişti. Geri kalanlar ise hem dürtüsel hem de önceden planlanmış saldırgan eylemlerde bulunanlar olarak ayrıldı. ASKB tanılı dürtüsel saldırganlığı olan hükümlülerin sözel becerileri daha zayıf, zirve P300 uyarılmış potansiyel amplitüdleri önemli ölçüde daha düşük saptanmıştır. Bu grupta antikonvülsan fenitoinin kullanımı ile saldırgan davranışta önemli bir azalma tespit edilmiştir[55].

ASKB'de dürtüsellik yaygın bir bulgudur, ancak dürtüsellik şiddeti bu bozukluğa sahip bireyler arasında değişebilir. ASKB olup dürtüsel saldırgan eylemlerde bulunanlar, bulunmayanlardan biyolojik olarak farklıdır. Ayrıca iki grup farmakolojik müdahaleye farklı yanıt verir. Coccaro ve ark. kişilik bozuklukları olan bireylerde serotonin salınımını artıran fenfluramine prolaktin yanıtının bu bireylerde dürtüsellik şiddeti ile anlamlı ilişkisi olduğunu göstermiştir[56]. ASKB ve dürtüsellik ilişkisini açıklamak için geniş çaplı farklı çalışmalara ihtiyaç duyulmaktadır.

Borderline (sınırda) kişilik bozukluğu

Dürtüsellik, BKB tanısının belirlenmesi için DSM-5 ölçütlerinden biridir. Hastalarda kontrolsüz harcama,

aşırı yeme veya tehlikeli cinsel davranış gibi dürtüsel eylemler duygusal stresle tetiklenir[57]. Links ve ark., BKB tanılı bireylerde uzun süreli bir izlem çalışması yürütmüş ve bu süreçte 'dürtüsel eylem' alt ölçeği skorlarının zaman içinde anlamlı bir değişim göstermediğini ortaya koymuştur. Bu bulgu, dürtüselliğin BKB'nin kalıcı ve yapısal bir özelliği olduğunu, hastalığın psikopatolojik çekirdeğinde yer aldığını düşündürmektedir[58].

BKB tanılı hastalarda intihar eğilimi ve dürtüselliğin değerlendirildiği çalışmalar mevcuttur. Soloff ve ark. bipolar depresyon tanılı ve unipolar depresyon tanılı olguları depresif ruh hali, umutsuzluk, dürtüsel saldırganlık ve intihar davranışı ölçümleri değerlendirdiğinde depresyon, dürtüsel saldırganlık ve umutsuzluk ölçümleri yüksek olan bireylerde daha fazla sayıda intihar girişimi olduğunu belirtmiştir[59].

Benzer şekilde, intihar girişimi öyküsü olan BKB tanılı olguların, intihar girişimi öyküsü olmayanlara kıyasla daha fazla dürtüsel davranışları olduğunu göstermiştir[60]. Mann ve ark. duygudurum bozuklukları, psikotik bozukluklar ve kaygı bozukluğu tanılı hastalarda hastalık tanısının intihar girişimleri üzerindeki etkisini araştırmış dürtüsel saldırganlık ve genel dürtüsellik ölçümleri yüksek olan hastalarda intihar girişiminin daha sık olduğunu bildirmiştir[61]. Psikiyatrik hastalığın şiddeti ile intihar girişimleri arasında anlamlı ilişki gösterilmemiştir. BKB tanılı hastalarda dürtüsellik intihar açısından önemli bir risk faktörü olarak görülmektedir.

Dougherty ve ark. BKB tanısıyla yatarak tedavi gören 14 kadın ve 17 karşılaştırma örneği için dürtüsel davranış ölçümleri yapmıştır[62]. BKB tanılı hastaların BIS-11 toplam puanlarının kontrol grubundan yüksek olduğu ve verilen görevlerde daha dürtüsel davranışlar sergilediklerini tespit etmiştir.

Özetle BKB'de dürtüsellik ve self-mutilatif davranışlar sık olarak gözlemlenir. Ayrıca BKB'de dürtüsellik, duygudurum düzensizliğinin bir parçasıdır[57]. Tedavi olarak da duygudurumu düzenlemeye yönelik Diyalektik Davranış Terapisi gibi terapötik yaklaşımlar ön plana çıkmaktadır[57].

Duygudurum Bozuklukları

Dürtüsellik Bipolar Bozukluk (BB) manik atağın DSM-5 tanı kriterlerinden biridir. BB atak dönemlerinde görülmesi şiddetle beklenen bir bulgudur[63]. BB manik dönemlerinde olduğu gibi depresif dönemlerinde görülen intihar girişimleri de kişinin dürtüselliği ile ilişkili görülmüştür[64].

BB manik atak dönemlerinde dikkat çekmekle birlikte hastalığın ötimik dönemlerinde de sağlıklı kontrollere kıyasla dürtüsellik ve öfke ölçümleri daha yüksektir[64]. Ayrıca dürtüsellik ölçümleri daha yüksek olan BB tanılı hastalarda olmayanlara göre daha fazla sayıda manik ve karma atak görülmektedir. Bu durum her ikisinin etiyolojisinde nöroadrenerjik aktivitenin rol alması ile açıklanmıştır[64].

Chan ve ark. yaptıkları bir güncel bir sistematik derlemede, BB'de dürtüsellikte rol oynayan bazı beyin bölgelerindeki işlevsel bozuklukların, duygudurumdan bağımsız olduğunu ve kalıcı olabileceğini ortaya koymuştur[65]. Bu çalışmada, BB tanılı hastalarda hızlı tepki inhibisyon görevlerinde frontal, singulat ve parietal bölgelerde azalmış aktivasyon görülürken, duygusal uyarana dayalı görevlerde aynı alanlarda aşırı aktivasyon saptanmıştır. Bu veriler, BB'de dürtüselliğin daha kompleks bir yapıda olduğunu düşündürmektedir.

Madde Kullanım Bozukluğu

Madde kullanımı, tamamen dürtüsellik ile açıklanamayacak karmaşık bir davranıştır. Madde kullanımı sonrası duyulan istek ve yoksunluk bağımlılığa yol açabildiği bilinmektedir ancak madde kullanımı olan kişiler sonuçlarını umursamadan hızlı ve plansız bir şekilde madde kullanmaktadır[63]. Dürtüsellik kesin olarak madde kullanımına neden olmasa da, dürtüsel davranışlarla suç işleyenlerde madde bağımlılığı genel nüfustan daha yüksektir[66]. Anket çalışmaları ile madde bağımlılığı olan bireylerde dürtüsellik ölçümlerinin sağlıklı kontrollerden anlamlı şekilde yüksek olduğu tekrar eden kez gösterilmiştir[67,68]. Ayrıca birden fazla maddeye bağımlılığı olan bireylerin tek bir maddeye bağımlılığı olanlara kıyasla dürtüsellik ölçümleri daha yüksektir[69,70]. Ödül-seçim yöntemini kullanan laboratuvar davranış çalışmalarında madde bağımlılığı öyküsü olan bireylerin hızlıca ödülü seçme eğiliminde olduklarını ve daha dürtüsel davrandıkları ortaya konmuştur[71,72].

Madde bağımlılığı gelişiminde dürtüsellik hem risk faktörü hem de bağımlılık sonucu artan bir özellik olarak görülür[16]. MKB'deki dürtüsellik üç faktörle açıklanmıştır: Zayıf bilişsel/inhibitör kontrol, madde

kullanımının beyin yapısına etkisi ve genetik/çevresel etkileşimler. Bu modele göre, dürtüsellik ve bağımlılık arasında özellikle frontostriatal devre bozukluğu gibi ortak nörobiyolojik mekanizmalar bulunmaktadır[16]. Bağımlılık tedavisinde dürtüselliği hedef alan farmakolojik ve davranışsal müdahaleler üzerinde yoğun araştırmalar sürmektedir.

Dikkat Eksikliği ve Hiperaktivite Bozukluğu

DSM-5 DEHB'yi dikkatsizlik, dürtüsellik ve hiperaktivite semptomlarını ayırarak tanımlamıştır. DEHB'de dürtüsellik temel semptomlardan biridir[73]. Dürtüsellik ve hiperaktivite alt tiplerinde bireylerde davranım bozukluğunun sık görüldüğü bildirilmiştir[63]. Çocuk yaşta dürtüsellik ve davranım bozukluğu olanların 18 yaş sonrası daha fazla suça karıştığı belirtilmiştir[74].

Davranış laboratuvarında sürekli performans testlerinde "dürtüsel" hata yapma sayısının DEHB tanılılarda kontrol grubuna göre yüksek saptanmıştır[75,76]. Marx ve arkadaşları yaptıkları bir meta-analizde DEHB'li bireylerin büyük-gecikmeli ödüller yerine daha küçük-anlık ödülleri tercih etme eğilimlerinin belirgin olduğunu bildirmiştir[73]. Ayrıca, DEHB tanılı erişkinlerde yapılan bir meta-analizde, stop-sinyal testi performansında belirgin inhibitör kontrol eksiklikleri saptanmış ve bu durumun bozukluğun karakteristik bir özelliği olabileceği belirtilmiştir[77].

DEHB tedavisinde kullanılan metilfenidat, atomoksetin gibi ilaçların dürtüselliği azaltıcı etkileri bilinmektedir ve yeni çalışmalar beyindeki glutamaterjik sistemin rolüne odaklanmıştır[78]. Dopaminerjik sisteme etki eden tedaviler ile dürtüsellik ve DEHB diğer bulgularının düzelmesi dürtüsellik, hiperaktivite ve dikkat sorunlarının dopaminerjik sistemle yakından ilişkili olduğunu göstermektedir.

Yeme Bozuklukları

Yeme bozukluklarında yeme davranışı denetiminde sorun görülmektedir. Bulimia nervoza vakalarında yeme davranışı üzerinde kontrol etme güçlüğü gözlenirken, anoreksiya nervoza hastalarında aşırı kontrol söz konusudur[79].

Dürtüsellik, yeme bozukluklarının seyrini olumsuz yönde etkilemektedir. Yeme bozukluklarında dürtüsellik genellikle tıkınırcasına yeme ve bulimia nervozada öne çıkan bir özelliktir. Olumsuz duygular karşısında dürtüsel davranma eğilimi, özellikle bulimia ve tıkınırcasına yeme bozukluğu ile kuvvetli ilişkili bulunmuştur[80]. Bu bozukluklarda dürtüsellik, kontrolsüz yeme atakları veya kendine zarar verme şeklinde ortaya çıkabilir.

Yeme bozukluğu olanlarda dürtüsellik, diğer dürtü denetimi sağlanamayan durumlar birlikte görülebilir. Bulimia nervozaya ek alkol kötüye kullanımı, ilaç kötüye kullanımı, özkıyım girişimi ve tekrarlayan kendine zarar verme davranışları ortaya çıkmaktadır[81,46]. Hem bulimia nervoza hem de anoreksiya nervoza vakalarında ve ailelerinde MKB, özkıyım girişimi gibi dürtüsellikle ilişkili durumlar daha sık görülmektedir[81,46].

Tanı Karmaşası ve Tedaviye Etkiler

Dürtüselliğin farklı psikiyatrik bozukluklarda ortak ancak değişken şekillerde ortaya çıkması, tanı sürecinde ayırt edici değil, karıştırıcı bir özellik haline gelmesine yol açmaktadır. Örneğin DEHB, BKB ve ASKB gibi bozuklukların tümü dürtüsellik barındırsa da, dürtüsel davranışların ortaya çıkış bağlamı, içsel motivasyonu ve sürekliliği farklılık göstermektedir[73]. Bu durum, özellikle eş tanı olasılığı yüksek bireylerde tanı koyma sürecini karmaşıklaştırmakta, zaman zaman yanlış tanı ve yetersiz müdahale riskini artırmaktadır[2].

Tedaviye yansımalar açısından dürtüsellik, ilaç uyumu, terapiye katılım, kriz anlarında riskli davranış olasılığı gibi birçok kritik klinik parametreyi etkilemektedir[64]. Örneğin DEHB'de dürtüsellik azaltıldığında yalnızca dikkat düzeyi değil, toplumsal uyum ve riskli davranış sıklığı da iyileşmektedir[77]. BKB tanılı bireylerde dürtüselliğin yüksek olması, intihar riski ve self-mutilatif davranışları artırarak tedavide daha yoğun izlem ve yapılandırılmış psikoeğitim gereksinimine işaret eder[58].

MKB tanılı bireylerde dürtüsellik hem bağımlılık gelişiminde bir risk faktörü, hem de yoksunluk döneminde kontrolsüz madde arayışını sürdüren bir etken olabilir[66]. Bu durum, sadece farmakoterapi değil aynı zamanda

dürtü kontrolünü hedefleyen bilişsel davranışçı müdahaleleri zorunlu hale getirmektedir. ASKB bireylerinde dürtüsellik, saldırganlık davranışlarının öngörülmesinde kritik bir biyobelirteç olabilir ve farmakolojik olarak serotonerjik ajanlara yanıt farklılığı dikkatle izlenmelidir[20].

Yeme bozuklukları söz konusu olduğunda, özellikle bulimia nervoza ve tıkınırcasına yeme bozukluğunda dürtüsellik, yalnızca yeme davranışını değil, komorbid özkıyım, madde kullanımı ve riskli cinsel davranışları da beraberinde getirebilir[80]. Bu klinik tablo, yalnızca yeme davranışına odaklanan terapilerin değil, duygusal regülasyon ve dürtüsellik hedefli bütüncül müdahalelerin gerekli olduğunu göstermektedir.

Dürtüselliğin psikiyatrik hastalıklarda görülme örüntüleri Tablo 1'de gösterilmektedir.

Tablo 1. Dürtüselliğin Psikiyatrik Hastalıklarda Görülme Örüntüleri

Psikiyatrik Hastalık	Baskın Dürtüsellik Türü	Ortaya Çıkış Biçimi	Tanısal Zorluk	Tedaviye Yansıma
Dikkat Eksikliği Hiperaktivite Bozukluğu	Motor + Bilişsel	Hızlı karar alma, acelecilik, sabırsızlık	Dikkatsizlikle karışabilir	İlaç uyumunu artırmak için dürtüsellik hedeflenir
Borderline Kişilik Bozukluğu	Emosyonel + Motor	Duygusal tetiklenme sonrası kendine zarar verme veya öfke patlamaları	Mani ile karışabilir, intihar riski örtüşebilir	Diyalektik davranış terapisi gibi yapılandırılmış terapi gerekir
Antisosyal Kişilik Bozukluğu	Motor + Saldırganlık temelli	Planlama eksikliği, ani saldırgan davranışlar	Planlı şiddetten ayrımı zor	Serotonin hedefli ilaçlara değişken yanıt
Madde Kullanım Bozukluğu	Motor + Ödül yönelimli	Anlık zevk arayışı, maddeye yönelim	Bağımlılık süreciyle iç içe geçmiş	Bilişsel davranışçı terapi ve farmakoterapi birlikte gerekir
Bulimia Nervoza	Emosyonel + Kontrolsüz yeme	Olumsuz duygular sonrası tıkınırcasına yeme	Normal aşırı yeme ile ayırt zor	Emosyon regülasyon temelli müdahale gerekir

Sonuç

Dürtüsellik, beyin yapıları, NT sistemleri ve genetik faktörlerle etkileşim halindedir. PFK ve OFK gibi beyin bölgeleri, dopamin, serotonin ve noradrenalin gibi NT'lerin rolü bu bağlamda önemlidir. Cinsiyet farklılıkları da dürtüselliğin gösterilme biçiminde etkili olup, erkekler somut ödüller karşısında daha fazla dürtüsellik sergileyebilirken, kadınlarda hormon seviyeleri ve evrimsel biyolojik faktörler bu durumu şekillendirir.

Dürtüsellik, psikiyatrik hastalıkların sınıflandırılmasında önemli bir yere sahiptir. BB, DEHB, OKB ve MKB gibi çeşitli psikiyatrik bozukluklar, dürtüselliğin belirgin şekilde görüldüğü durumlardır. Ancak dürtüsellik, tek başına bir tanı kriteri olmamakta ve eşlik eden diğer belirtilerle birlikte değerlendirilerek klinik tanı konulmaktadır. Bununla birlikte, dürtüsellik, ASKB ve BKB gibi kişilik bozukluklarıyla da ilişkilendirilebilmektedir. Bu nedenle dürtüselliğin doğru ve çok boyutlu değerlendirilmesi, yalnızca tanısal süreçleri değil; aynı zamanda tedavi planlamasını, olası nükslerin önlenmesini ve bireyselleştirilmiş müdahale stratejilerinin oluşturulmasını da doğrudan etkilemektedir.

Sonuç olarak dürtüsellik çok boyutlu ve kompleks bir davranış örüntüsü olup, psikiyatrik bozuklukların anlaşılmasında önemli bir yer tutmaktadır. Bu alanda yapılacak ileri araştırmalar, dürtüselliğin biyolojik temellerinin ve psikiyatrik bozukluklardaki rolünün daha iyi anlaşılmasına katkı sağlayacaktır ve tedavi yaklaşımlarının iyileştirilmesi açısından büyük önem taşımaktadır.

Kaynaklar

1. Moore FR, Doughty H, Neumann T, McClelland H, Allott C, O'Connor RC. Impulsivity, aggression, and suicidality relationship in adults: a systematic review and meta-analysis. EClinicalMedicine. 2022;45.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Washington DC, American Psychiatric Association, 2013.
3. Nigg JT. Annual Research Review: On the relations among self-regulation, self-control, executive functioning, effortful control, cognitive control, impulsivity, risk-taking, and inhibition for developmental psychopathology. J Child Psychol Psychiatry. 2017;58:361-83.
4. Eysenck SBG, Eysenck HJ. The place of impulsiveness in a dimensional system of personality description. Br J Soc Clin Psychol. 1977;16:57-68.
5. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995;51:768-74.
6. Ainslie G. Specious reward: a behavioral theory of impulsiveness and impulse control. Psychol Bull. 1975;82:463.
7. Hollander E, Evers M. New developments in impulsivity. Lancet. 2001;358:949-50.
8. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. Am J Psychiatry. 2001;158:1783-93.
9. Stahl C, Voss A, Schmitz F et al. Behavioral components of impulsivity. J Exp Psychol Gen. 2014;143:850.
10. Cross CP, Copping LT, Campbell A. Sex differences in impulsivity: a meta-analysis. Psychol Bull. 2011;137:97.
11. Huang Y, Luan S, Wu B, et al. Impulsivity is a stable, measurable, and predictive psychological trait. Proc Natl Acad Sci USA. 2024;121:e2321758121.
12. L'Abate L. A family theory of impulsivity. In: The impulsive client: Theory, research, and treatment. 1st ed. Ed(s): McCown WG, Johnson JL, Shure MB: Washington, DC, American Psychological Association, 1993;93-117.
13. Barratt ES, Stanford MS, Kent TA, Alan F. Neuropsychological and cognitive psychophysiological substrates of impulsive aggression. Biol Psychiatry. 1997;41:1045-61.
14. Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sci. 1983;33:2609-14.
15. Barratt ES, Stanford MS, Felthous AR, Kent TA. The effects of phenytoin on impulsive and premeditated aggression: a controlled study. J Clin Psychopharmacol. 1997;17:341-49.
16. Raji H, Dinesh S, Sharma S. Inside the impulsive brain: a narrative review on the role of neurobiological, hormonal and genetic factors influencing impulsivity in psychiatric disorders. Egypt J Neurol Psychiatr Neurosurg. 2025;61:4.
17. Hüpen P, Kumar H, Müller D, Swaminathan R, Habel U, Weidler C. Functional brain network of trait impulsivity: whole-brain functional connectivity predicts self-reported impulsivity. Hum Brain Mapp. 2024;45:e70059.
18. Yazici K, Yazici AE. Dürtüselligin nöroanatomik ve nörokimyasal temelleri. Psikiyatride Guncel Yaklaşımlar. 2010;2:254-280.
19. Åsberg M, Träskman L, Thorén P. 5-HIAA in the cerebrospinal fluid: A biochemical suicide predictor? Arch Gen Psychiatry. 1976;33:1193-97.
20. Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sci. 1983;33:2609-14.
21. Virkkunen M, Rawlings R, Tokola R, et al. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. Arch Gen Psychiatry. 1994;51:20-7.
22. Tyano S, Zalsman G, Ofek H, et al. Plasma serotonin levels and suicidal behavior in adolescents. European Neuropsychopharmacology. 2006;16:49-57.
23. Biederman J, Mick E, Surman C et al. A randomized, placebo-controlled trial of OROS methylphenidate in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2006;59:829-35.
24. Robinson EJ, Eagle DM, Bannerjee G, Robbins TW. Effects of atomoxetine on inhibitory control in the rat stop-signal task. J Psychopharmacol. 2006;20:A67.
25. Blondeau C, Dellu-Hagedorn F. Dimensional analysis of ADHD subtypes in rats. Biol Psychiatry. 2007;61:1340-50.
26. Thomason C, Michelson D. Atomoxetine--treatment of attention deficit hyperactivity disorder: beyond stimulants. Drugs Today (Barc). 2004;40:465-73.
27. Greenhill LL, Biederman J, Boellner SW et al. A randomized, double-blind, placebo-controlled study of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45:503-11.
28. Green R, Meredith LR, Mewton L, Squeglia LM. Adolescent neurodevelopment within the context of impulsivity and substance use. Curr Addict Rep. 2023;10:166-77.
29. Kruger DJ, Nesse RM. An evolutionary life-history framework for understanding sex differences in human mortality rates. Hum Nat. 2006;17:74-97.
30. Cross CP, Copping LT, Campbell A. Sex differences in impulsivity: a meta-analysis. Psychol Bull. 2011;137:97.
31. Wilson M, Daly M. Competitiveness, risk taking, and violence: The young male syndrome. Ethol Sociobiol. 1985;6:59-73.
32. Abbott MS, Seaman Jr RW, Doyle MR, Maguire DR, Rice KC, Collins GT. Interactions between impulsivity and MDPV self-administration in rats. Addiction biology. 2022;27:e13168.
33. Boonstra AM, Oosterlaan J, Sergeant JA, Buitelaar JK. Executive functioning in adult ADHD: a meta-analytic review. Psychol Med. 2005;35:1097-1108.
34. Lijffijt M, Kenemans JL, Verbaten MN, van Engeland H. A meta-analytic review of stopping performance in attention-deficit/hyperactivity disorder: deficient inhibitory motor control? J Abnorm Psychol. 2005;114:216.

35. Uhre VF, Larsen KM, Herz DM, Baaré W, Pagsberg AK, Siebner HR. Inhibitory control in obsessive compulsive disorder: A systematic review and activation likelihood estimation meta-analysis of functional magnetic resonance imaging studies. Neuroimage Clin. 2022;36:103268.
36. Chamberlain SR, Fineberg NA, Blackwell AD, Robbins TW, Sahakian BJ. Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. American journal of psychiatry. 2006;163:1282-84.
37. Penades R, Catalan R, Rubia K, Andres S, Salamero M, Gasto C. Impaired response inhibition in obsessive compulsive disorder. European Psychiatry. 2007;22:404-10.
38. Monterosso JR, Aron AR, Cordova X, Xu J, London ED. Deficits in response inhibition associated with chronic methamphetamine abuse. Drug Alcohol Depend. 2005;79:273-77.
39. Eysenck SBG, Pearson PR, Easting G, Allsopp JF. Age norms for impulsiveness, venturesomeness and empathy in adults. Pers Individ Dif. 1985;6:613-19.
40. Matthys W, Van Goozen SHM, De Vries H, Cohen-Kettenis PT, Van Engeland H. The dominance of behavioural activation over behavioural inhibition in conduct disordered boys with or without attention deficit hyperactivity disorder. J Child Psychol Psychiatry. 1998;39:643-51.
41. Halperin JM, Wolf LE, Pascualvaca DM, et al. Differential assessment of attention and impulsivity in children. J Am Acad Child Adolesc Psychiatry. 1988;27:326-29.
42. Dougherty DM, Moeller FG, Steinberg JL, Marsh DM, Hines SE, Bjork JM. Alcohol increases commission error rates for a continuous performance test. Alcohol Clin Exp Res. 1999;23:1342-51.
43. Evenden JL. The pharmacology of impulsive behaviour in rats VII: the effects of serotonergic agonists and antagonists on responding under a discrimination task using unreliable visual stimuli. Psychopharmacology (Berl). 1999;146:422-31.
44. Puumala T, Sirviö J. Changes in activities of dopamine and serotonin systems in the frontal cortex underlie poor choice accuracy and impulsivity of rats in an attention task. Neuroscience. 1998;83:489-99.
45. Lamichhane B, Moukaddam N, Salas R, Goodman W, Sabharwal A. Multimodal objective assessment of impulsivity in healthy and mood disorder participants. NPP Digit Psychiatry Neurosci. 2025;3:6.
46. Özdemir PG, Selvi Y, Aydin A. Dürtüsellik ve tedavisi. Psikiyatride Güncel Yaklaşımlar. 2012;4:293-314.
47. Tamam L, Döngel B. Yıkıcı bozukluklar, dürtü kontrol ve davranım bozuklukları. In: Temel ve Klinik Psikiyatri. 1st ed. Ankara, Güneş Yayınevi. 2018.
48. Cuthbert BN, Insel TR. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC Med. 2013;11:1-8.
49. Gray JA. A model of the limbic system and basal ganglia: Applications to anxiety and schizophrenia. In: The Cognitive Neurosciences. 1st ed. Ed: Gazzaniga MS: Cambridge (MA), The MIT Press, 1995;1165-1176.
50. Rachlin H. The Science of Self-Control. Cambridge (MA), Harvard University Press, 2004.
51. Damasio AR, Tranel D, Damasio H. Individuals with sociopathic behavior caused by frontal damage fail to respond autonomically to social stimuli. Behavioural brain research. 1990;41:81-94.
52. Swann AC, Janicak PL, Calabrese JR, et al. Structure of mania: subgroups with distinct clinical characteristics and course of illness in randomized clinical trial participants. J Affect Disord. 2001;67:123-32.
53. Marzilli E, Cerniglia L, Cimino S. Antisocial personality problems in emerging adulthood: The role of family functioning, impulsivity, and empathy. Brain Sci. 2021;11:687.
54. Barratt ES, Stanford MS, Kent TA, Alan F. Neuropsychological and cognitive psychophysiological substrates of impulsive aggression. Biol Psychiatry. 1997;41:1045-61.
55. Barratt ES, Stanford MS, Felthous AR, Kent TA. The effects of phenytoin on impulsive and premeditated aggression: a controlled study. J Clin Psychopharmacol. 1997;17:341-49.
56. Coccaro EF, Siever LJ, Klar HM, et al. Serotonergic studies in patients with affective and personality disorders: correlates with suicidal and impulsive aggressive behavior. Arch Gen Psychiatry. 1989;46:587-99.
57. Leichsenring F, Fonagy P, Heim N, et al. Borderline personality disorder: a comprehensive review of diagnosis and clinical presentation, etiology, treatment, and current controversies. World Psychiatry. 2024;23:4-25.
58. Links PS, Heslegrave R, Reekum R van. Impulsivity: core aspect of borderline personality disorder. J Pers Disord. 1999;13:1-9.
59. Soloff PH, Lynch KG, Kelly TM, Malone KM, Mann JJ. Characteristics of suicide attempts of patients with major depressive episode and borderline personality disorder: a comparative study. Am J Psychiatry. 2000;157:601-8.
60. Soloff PH, Lis JA, Kelly T, Cornelius J, Ulrich R. Risk factors for suicidal behavior in borderline personality disorder. Am J Psychiatry. 1994;151:1316-23.
61. Mann JJ, Waternaux C, Haas GL, Malone KM. Toward a clinical model of suicidal behavior in psychiatric patients. American journal of Psychiatry. 1999;156:181-89.
62. Dougherty DM, Bjork JM, Huckabee HCG, Moeller FG, Swann AC. Laboratory measures of aggression and impulsivity in women with borderline personality disorder. Psychiatry Res. 1999;85:315-26.
63. Moeller FG, Barratt ES, Dougherty DM, Schmitz JM, Swann AC. Psychiatric aspects of impulsivity. American journal of psychiatry. 2001;158:1783-93.
64. Özdemir PG, Selvi Y, Aydin A. Dürtüsellik ve tedavisi. Psikiyatride Güncel Yaklaşımlar. 2012;4:293-314.
65. Chan CC, Alter S, Hazlett EA, et al. Neural correlates of impulsivity in bipolar disorder: A systematic review and clinical implications. Neurosci Biobehav Rev. 2023;147:105109.
66. Brady KT, Myrick H, McElroy S. The relationship between substance use disorders, impulse control disorders, and pathological aggression. American Journal on Addictions. 1998;7:221-30.
67. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. J Clin Psychol. 1995;51:768-74.
68. Allen TJ, Moeller FG, Rhoades HM, Cherek DR. Impulsivity and history of drug dependence. Drug Alcohol Depend. 1998;50:137-145.

69. McCown WG. Multi-impulsive personality disorder and multiple substance abuse: evidence from members of self-help groups. Br J Addict. 1988;83:431-32.
70. O'Boyle M, Barratt ES. Impulsivity and DSM-III-R personality disorders. Pers Individ Dif. 1993;14:609-11.
71. Kirby KN, Petry NM, Bickel WK. Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. J Exp Psychol Gen. 1999;128:78.
72. Mitchell SH. Measures of impulsivity in cigarette smokers and non-smokers. Psychopharmacology (Berl). 1999;146:455-64.
73. Marx I, Hacker T, Yu X, Cortese S, Sonuga-Barke E. ADHD and the choice of small immediate over larger delayed rewards: a comparative meta-analysis of performance on simple choice-delay and temporal discounting paradigms. J Atten Disord. 2021;25:171-87.
74. Babinski LM, Hartsough CS, Lambert NM. Childhood conduct problems, hyperactivity-impulsivity, and inattention as predictors of adult criminal activity. J Child Psychol Psychiatry. 1999;40:347-55.
75. O'Toole K, Abramowitz A, Morris R, Dulcan M. Effects of methylphenidate on attention and nonverbal learning in children with attention-deficit hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 1997;36:531-38.
76. Halperin JM, Wolf LE, Pascualvaca DM et al. Differential assessment of attention and impulsivity in children. J Am Acad Child Adolesc Psychiatry. 1988;27:326-29.
77. Senkowski D, Ziegler T, Singh M et al. Assessing inhibitory control deficits in adult ADHD: A systematic review and meta-analysis of the stop-signal task. Neuropsychol Rev. 2024;34:548-67.
78. Bauer J, Werner A, Kohl W et al. Hyperactivity and impulsivity in adult attention-deficit/hyperactivity disorder is related to glutamatergic dysfunction in the anterior cingulate cortex. The world journal of biological psychiatry. 2018;19:538-46.
79. Camacho-Barcia L, Giel KE, Jiménez-Murcia S, et al. Eating disorders and obesity: bridging clinical, neurobiological, and therapeutic perspectives. Trends Mol Med. 2024;30:361-379.
80. Davis HA, Smith GT. Examining the role of urgency in predicting binge size in bulimia nervosa. Front Psychol. 2023;14:1166119.
81. Welch SL, Fairburn CG. Impulsivity or comorbidity in bulimia nervosa: A controlled study of deliberate self-harm and alcohol and drug misuse in a community sample. Br J Psychiatry. 1996;169:451-58.

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Farmakovijilans Önemi: Kozmetovijilans

İmportance of Pharmacovigilance: Cosmetovigilance

Yusuf Karataş[1], Gülcan Tanrıkulu Kayan[1]

[1]Çukurova Üniversitesi Tıp Fakültesi, Tıbbi Farmakoloji Anabilim Dalı, Adana, Türkiye

ABSTRACT
Pharmacovigilance is defined as a scientific discipline that involves the monitoring, detection, assessment, and prevention of adverse effects associated with drug use, as well as the investigation of whether these effects are causally related to the administered drug. Cosmetovigilance encompasses the scientific and regulatory processes aimed at monitoring, evaluating, and preventing undesirable effects arising from the normal or reasonably foreseeable use of cosmetic products. Reports of adverse effects associated with cosmetic use have become increasingly prominent in recent years. However, due to factors such as underreporting, system deficiencies, and low user awareness, the effectiveness of current cosmetovigilance systems remains limited. The growing prevalence of dermocosmetic practices further underscores the need for more stringent oversight in this field. Cosmetovigilance represents a critical discipline for the protection of public health. Strengthening healthcare systems with the support of competent authorities, improving the training of healthcare professionals, and developing effective feedback mechanisms will contribute to enhancing cosmetic safety.
Keywords: Pharmacovigilance, cosmetovigilance, adverse drug reactions, public health, product safety

ÖZET
Farmakovijilans, ilaç kullanımıyla ortaya çıkabilen advers etkilerin izlenmesi, tespit edilmesi, değerlendirilmesi, önlenmesi ve bu etkilerin gerçekten ilacın alınması ile nedensel ilişkisinin olup olmadığını araştıran bir bilim dalı olarak tanımlanmaktadır. Kozmetovijilans, kozmetik ürünlerin normal ya da öngörülebilir kullanım koşulları altında ortaya çıkan istenmeyen etkilerinin izlenmesi, değerlendirilmesi ve önlenmesine yönelik bilimsel ve düzenleyici süreçleri kapsar. Kozmetik ürünlerin kullanımına bağlı advers etkiler özellikle son yıllarda artan bildirimlerle dikkat çekmektedir. Ancak bildirimin azlığı, sistem eksiklikleri ve kullanıcı farkındalığının düşüklüğü gibi nedenlerle mevcut kozmetovijilans sistemlerinin etkinliği sınırlı kalmıştır. Dermokozmetik uygulamaların yaygınlaşması da bu alandaki denetim ihtiyacını artırmaktadır. Kozmetovijilans, halk sağlığını korumaya yönelik önemli bir disiplindir. Yetkili kuruluşların desteği ile sağlık sistemlerin güçlendirilmesi, sağlık profesyonellerinin eğitimi ve geri bildirim mekanizmalarının geliştirilmesi, kozmetik güvenliğinin artırılmasına katkı sağlayacaktır.
Anahtar kelimeler: Farmakovijilans, kozmetovijilans, advers ilaç reaksiyonu, halk sağlığı, ürün güvenliği

Giriş

Farmakovijilans, ilaç kullanımıyla ortaya çıkabilen advers etkilerin izlenmesi, tespit edilmesi, değerlendirilmesi, önlenmesi ve bu etkilerin gerçekten ilacın alınması ile nedensel ilişkisinin olup olmadığını araştıran bir disiplin olarak tanımlanmaktadır. Farmakovijilansın kapsamı son yıllarda önemli ölçüde genişlemiştir[1]. Dünya Sağlık Örgütü (DSÖ), farmakovijilansı "hasta güvenliğini artırmak için yan etkilerin veya diğer olası ilaçla ilgili sorunların tespiti, değerlendirilmesi, anlaşılması ve önlenmesiyle ilgili bilim ve faaliyetler" olarak tanımlamaktadır. Bu faaliyetler, hem bireysel hasta seviyesinde hem de toplumsal düzeyde rasyonel tedavi uygulamalarını destekler[2]. Küresel düzeyde, ilaç kullanımının neden olabileceği sonuçların ve advers etkilerin kontrol altına alınması için farmakovijilans sistemleri her geçen gün daha da geliştirilmektedir. Ancak, son yıllarda sadece ilaçlar değil, aynı zamanda yaygın olarak kullanılan kozmetik ürünlerin de yan etkilere neden olabileceği fark edilmiştir. Bu durum, farmakovijilans kavramının ardından "kozmetovijilans" kavramını ortaya çıkarmış; kozmetik ürünlerin güvenliğini ele almak için istenmeyen

Correspondence Address / Yazışma Adresi
Yusuf Karataş, Çukurova Üniversitesi Tıp Fakültesi, Tıbbi Farmakoloji Anabilim Dalı, Adana, Türkiye e-mail: ykaratas@cu.edu.tr

2025;34(3):209-212
doi:10.17827/aktd.1687716
Geliş tarihi/ Received: 30.04.2025
Kabul tarihi/Accepted: 26.08.2025

etkilerin bildirilmesi ve izlenmesiyle ilgili faaliyetleri yönetmek amacıyla bir disiplin oluşturma ihtiyacını da beraberinde getirmiştir[3]. Kozmetik ürünler, günlük yaşamda estetik amaçlarla yaygın şekilde kullanılan; cilt, saç, tırnak gibi vücudun dış yüzeylerine uygulanan ürünlerdir. Ancak bu ürünlerin içerdiği kimyasallar bazen cilt yapısına zararlı etkiler (irritasyon), alerjik reaksiyonlar ve nadir de olsa sistemik toksisiteler gibi önemli advers etkilere yol açabilmektedir. Bu nedenle, kozmetik ürünlerin güvenliği de en az ilaçlar kadar dikkatle izlenmelidir[2]. Bu çalışmada, farmakovijilansın bir dalı olan kozmetovijilansın halk sağlığı bakımından taşıdığı önemi hakkında bilgi verilmesi, kozmetik advers etkiler sonrası davranış ve tutumlar hakkında farkındalık oluşturulması amaçlanmıştır.

Farmakovijilans Tanımı ve Fonksiyonları

Farmakovijilans, tıbbi ürünlerin güvenlik profilini izlemeye yönelik sistematik bir yaklaşımdır ve çok boyutlu bir yapıya sahiptir. Klinik çalışmalardan pazarlama sonrası kullanıma kadar uzanan süreçte, advers ilaç reaksiyonlarının (AİR) ve diğer ilaçla ilgili problemlerin tanımlanması, izlenmesi, analiz edilmesi ve önlenmesi hedeflenmektedir. Bu kapsamda farmakovijilans; ürün güvenliğinin izlenmesi, risk-fayda oranının değerlendirilmesi, yeni risklerin tanımlanması, uygun risk yönetimi stratejilerinin uygulanması ve bu bilgilerin sağlık profesyonelleri ve kamu ile etkin bir şekilde paylaşılması gibi temel fonksiyonlara sahiptir[4]. Farmakovijilans faaliyetleri, yalnızca ilaç endüstrisini değil; ayrıca klinik uygulamaları ve halk sağlığı politikalarını da doğrudan etkiler. WHO-Uppsala Monitoring Centre tarafından yürütülen VigiBase gibi uluslararası veri tabanları, farklı ülkelerden bildirilen AİR vakalarını toplayarak dünyadaki genel güvenlik durumunu analiz etmeye olanak tanımaktadır. Bu sistemler sayesinde çok nadir ama ciddi advers reaksiyonlar dahi tespit edilebilir hale gelmiştir[5]. Farmakovijilans, hastanın tedaviye verdiği cevabın sadece etkinlik boyutuyla değil, aynı zamanda güvenlilik boyutuyla da değerlendirilmesini sağlamaktadır. Bu nedenle akılcı ilaç kullanımının temel taşlarından biri olup, hasta güvenliğini ön planda tutan modern sağlık sistemlerinde vazgeçilmez bir yere sahiptir[6].

Kozmetovijilansın Kapsamı ve Gelişimi

DSÖ'nün tanımına göre; Kozmetovijilans, kozmetik ürünlerin kullanımına bağlı olarak ortaya çıkan istenmeyen etkilerin (advers etkilerin) tespiti, değerlendirilmesi, izlenmesi ve önlenmesi ile ilgilenen halk sağlığı temelli bir gözetim sistemidir. DSÖ ve Avrupa Birliği düzenlemeleri doğrultusunda, kozmetik ürünlerin güvenliği artık sadece üretim aşamasıyla sınırlı görülmemekte; aynı zamanda tüketici ürünlerinin güvenliği ve kozmetik ürünlerin halk sağlığına etkileri konularında çalışmalar yürütmekte, kozmetovijilans uygulamalarını pazarlama sonrası gözetim süreçleriyle desteklemektedir[5]. Kozmetovijilans kavramı ilk kez 2000'li yılların başında Fransa'da uygulamaya geçirilmiş ve kısa sürede Avrupa'da birçok ülke tarafından benimsenmiştir. Avrupa Birliği'nin 1223/2009 sayılı Kozmetik Regülasyonu, kozmetik ürünlerin güvenlik değerlendirmesini zorunlu kılmakta ve ciddi istenmeyen etkilerin raporlanmasını kozmetik ürün üreticilerine ve yetkili kuruluşlara yükümlülük olarak getirmektedir. Türkiye'de ise kozmetovijilans faaliyetleri, Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK) tarafından yürütülmektedir[6]. TİTCK, kozmetik ürünlerin güvenli şekilde kullanımlarının sağlanması için advers etkilerin izlenmesi ve kozmetik ürünlerin yol açabileceği zararın en az düzeye indirilmesi için gerekli tedbirlerin alınması amacıyla çalışmalar yürütmektedir. Piyasada yer alan kozmetik ürünlerin, güvenlilik çalışmaları dahil, kozmetovijilans etkinlikleri ile ilgili olarak ulaşan advers etki bildirimleri, bilgiler ve raporlar TİTCK tarafından değerlendirilmekte, gerekli hallerde Bilimsel Danışma Komisyona sunularak görüş alınmaktadır. Ciddi istenmeyen yan etkiler ve alınan tedbirler TİTCK resmi internet sayfasından duyurulmaktadır[7].

Kozmetik Ürünlere Bağlı Gelişen Advers Reaksiyonlar ve Bildirimi

TİTCK 5324 sayılı Kozmetik Kanunu'nun 4. maddesinin (d) bendi ve Kozmetik Yönetmeliği'nin 6. maddesi gereğince; Piyasaya arz edilen bir kozmetik ürün, normal ve üretici tarafından öngörülebilen şartlar altında uygulandığında veya ürünün sunumu, etiketlenmesi, kullanımına dair açıklamalara veya üretici tarafından sağlanan bilgiler dikkate alınarak önerilen kullanım şartlarına göre uygulandığında, insan sağlığı açısından güvenli olmalıdır[8]. Bu reaksiyonlar genellikle geçici ve hafif olsa da, bazı durumlarda sistemik etkiler ya da kalıcı hasarlar söz konusu olabilir[9,10] .Kozmetovijilans sistemlerinin etkinliği, doğru ve zamanında bildirimlere bağlıdır. Ancak mevcut sistemlerde kullanıcı farkındalığının düşük olması, bildirimlerin

yetersizliğine yol açmaktadır[11]. Ayrıca, üretici firmaların şeffaf bildirim yapma sorumluluklarını yeterince yerine getirmemesi ve yetkili kuruluşlar arasındaki iletişim eksiklikleri, sistemin zayıf işlemesine neden olmaktadır[2]. Dermokozmetik ürünler ve uygulamalar, kozmetovijilans sistemlerinde özel olarak değerlendirilmesi gereken alanlardır. Botoks, dolgu, mezoterapi gibi uygulamalar sonrasında da advers etkiler meydana gelebilmekte ve bu etkiler zaman zaman ciddi komplikasyonlara sebep olabilmektedir. Bu nedenle, bu uygulamalara ilişkin özel izleme ve raporlama sistemleri geliştirilmelidir[6,12].

Kozmetovijilansın Halk Sağlığı Açısından Önemi

Kozmetovijilans, yalnızca bireysel güvenliği değil, aynı zamanda halk sağlığını korumaya yönelik stratejik bir araçtır. Toplumun her kesiminin maruz kaldığı kozmetik ürünlerin denetimi ve güvenliğinin sağlanması, önlenebilir sağlık sorunlarının azaltılmasında önemli rol oynar. Bu nedenle kozmetovijilans, sağlık politikalarının ayrılmaz bir parçası olarak değerlendirilmelidir[3,13]. Dünya genelinde artan kozmetik tüketimi, bu ürünlerin güvenliliğine yönelik düzenleyici sistemlerin önemini her geçen gün artırmaktadır. Kozmetovijilans, kozmetik ürünlere bağlı istenmeyen / ciddi istenmeyen etkilerin spontan bildirimlerinin toplanmasını, değerlendirilmesini ve izlenmesini kapsayan bilimsel bir süreçtir. Kozmetik ürünlerin olası advers etkilerinin test edilmesine ve izlenmesine yönelik komzetovijilans çalışmaları günden güne daha fazla önem kazanmaktadır. Yapılan çalışmalar, kozmetik ürünlerde bulunan çeşitli kimyasal maddelere maruz kalmanın sağlık açısından risk oluşturabileceğini ortaya koymuştur[13].

Avrupa Birliği'nde yürürlüğe giren 1223/2009 sayılı Kozmetik Ürünler Yönetmeliği, kozmetovijilans sistemlerini zorunlu hale getirerek üreticilerin advers etkileri Ulusal Yetkili Mercilere bildirmesini şart koşmuştur. Bu düzenleme, ciddi advers etkilerin merkezi bir veri tabanında toplanmasını ve halk sağlığının korunması için gerekli düzenleyici müdahalelerin zamanında yapılabilmesini sağlamaktadır (European Commission, 2013). ABD'de ise FDA, kozmetik ürünlere ilişkin istenmeyen etkilerin MedWatch sistemi üzerinden bildirilmesini teşvik etmektedir; ancak bu sistem hâlen gönüllülüğe dayalıdır ve bu durum yetersiz bildirim sorununu beraberinde getirmektedir[14]. Kozmetovijilans sistemlerinin etkinliği, yalnızca yasal çerçevelerin varlığıyla sınırlı değildir; aynı zamanda sağlık profesyonellerinin ve kullanıcıların farkındalığı, bildirimin teşvik edilmesi ve verilerin analitik olarak değerlendirilmesi gibi çok boyutlu bir yaklaşımı gerekli kılar. Bildirim eksikliği, potansiyel halk sağlığı tehditlerinin geç tanımlanmasına veya hiç fark edilmemesine neden olabilmektedir[15]. Bu durum, özellikle kozmetik ürünlerin yaygın kullanıldığı günümüzde daha da önemli hale gelmektedir. Sağlık sistemlerinin güçlendirilmesi, sorumlu kuruluşların aktif desteği, sağlık profesyonellerinin eğitimi ve kullanıcı farkındalığının artırılması gibi çok yönlü gelişimlerle desteklenen bir kozmetovijilans yaklaşımı, toplum genelinde kozmetik ürünlerin güvenli kullanımını teşvik edecek ve halk sağlığının sürdürülebilirliğine katkı sağlayacaktır[12].

Sonuç ve Öneriler

Kozmetik ürünlerin güvenliğine ilişkin farkındalığın artması ve bu ürünlerle ilişkili advers etkilerin sistematik biçimde izlenmesi, farmakovijilansın bir disiplini olan kozmetovijilansın önemini her geçen gün daha da artırmaktadır. Bu bağlamda, kozmetovijilans sistemlerinin etkin bir şekilde işletilmesi, kamu sağlığını korumak açısından temel bir gereklilik haline gelmiştir[15].

Sağlık profesyonellerinin ve tüketicilerin advers reaksiyonları bildirme konusunda eğitilmesi, bildirim sistemlerinin dijital teknolojilerle desteklenerek erişilebilirliğinin artırılması ve üretici firmaların yasal yükümlülüklerinin denetlenmesi önem kazanmaktadır. Ayrıca, dermokozmetik uygulamaların da bu sistemlere dahil edilmesi gerekmektedir[16].

Sonuç olarak, kozmetovijilans yalnızca advers etki bildiriminden ibaret bir mekanizma değil; ürün güvenliği, hasta hakları, sağlık sistemlerinin sürdürülebilirliği ve toplum sağlığının korunması açısından bütüncül bir yaklaşımı temsil etmektedir. Bu nedenle, kozmetovijilans uygulamalarının güçlendirilmesi ve yaygınlaştırılması, hem ulusal hem de küresel ölçekte halk sağlığını güvence altına almanın anahtar unsurlarından biri olmalıdır[17].

Kaynaklar

1. Khan Z, Karataş Y, Rahman H. Adverse drug reactions reporting in Turkey and barriers: an urgent need for pharmacovigilance education. Ther Adv Drug Saf. 2020;11:2042098620922483.
2. Toklu HZ, Antigua A, Lewis V, Reynolds M, Jones J. Cosmetovigilance: A review of the current literature. J Fam Med Prim Care. 2019;8:1540–5.
3. Lucca JM, Joseph R, Hussain Al Kubaish Z, Mohammad Al-Maskeen S, Ali Alokaili Z. An observational study on adverse reactions of cosmetics: The need of practice the Cosmetovigilance system. Saudi Pharm J. 2020;28:746–53.
4. Jose J, Rubaie MHA, Ramimy HA, Varughese SS. Pharmacovigilance. Sultan Qaboos Univ Med J. 2021;21:e161–3.
5. Vigan M, Castelain F. Cosmetovigilance: definition, regulation and use "in practice". Eur J Dermatol. 2014;24:643–9.
6. Altiokka İ, Üner M. Safety in cosmetics and cosmetovigilance, current regulations in Türkiye. Turk J Pharm Sci. 2022;19:610–7.
7. Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK). Kozmetik ürün güvenlilik değerlendiricisine, eğitimine ve belgelendirilmesine ilişkin kılavuz [Internet]. 2024 Mar 22 [cited 2025 Jul 31]. Available from: https://www.titck.gov.tr/mevzuat/kozmetik-urun-guvenlilik-degerlendiricisine-egitimine-ve-belgelendirilmesine-iliskin-kilavuz-22032024105525.
8. Türkiye İlaç ve Tıbbi Cihaz Kurumu (TİTCK). 5324 sayılı Kozmetik Kanunu ve Kozmetik Yönetmeliği [Internet]. Ankara: TİTCK; 2024 [cited 2025 Jul 31]. Available from: https://www.titck.gov.tr/mevzuat.
9. Berne B, Tammela M, Färm G, Inerot A, Lindberg M. Can the reporting of adverse skin reactions to cosmetics be improved? A prospective clinical study using a structured protocol. Contact Dermatitis. 2008;58:223–7.
10. Bilal AI, et al. Cosmetics use-related adverse events and determinants among Jigjiga town residents, Eastern Ethiopia. Dermatol Ther. 2017;7:143–53.
11. J SS, et al. A comparative analysis of cosmetovigilance frameworks in key regions: Europe, the United States, Japan, and India. Afr J Biomed Res. 2024;27:doi:10.53555/AJBR.v27i4S.5873.
12. Praveen J, Swaminathan TV. Cosmetovigilance: Emerging safety trends. Indian J Pharm Pharmacol. 2023;10:132–41.
13. Sautebin L. A cosmetovigilance survey in Europe. Pharmacol Res. 2007;55:455–60.
14. U.S. Food and Drug Administration (FDA). Adverse event reporting for cosmetics [Internet]. Silver Spring (MD): FDA; 2020 [cited 2025 Apr 29]. Available from: https://www.fda.gov/cosmetics/cosmetics-recalls-alerts/adverse-event-reporting-cosmetics.
15. Darbre PD, Harvey PW. Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. J Appl Toxicol. 2008;28:561–78.
16. Vigan M. [New allergens in cosmetics. Cosmetovigilance]. Ann Dermatol Venereol. 1997;124:571–5.
17. U.S. Food and Drug Administration (FDA). Modernization of cosmetics regulation act of 2022 (MoCRA) – overview of key provisions [Internet]. Silver Spring (MD): FDA; 2023 [cited 2025 Apr 22]. Available from: https://www.fda.gov/cosmetics/cosmetics-laws-regulations/modernization-cosmetics-regulation-act-2022-mocra.

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Pediatric Intraoperative Fluid Therapy in Anesthesiology

Anesteziyolojide Pediatrik İntraoperatif Sıvı Tedavisi

Ersel Güleç[1]

[1]Cukurova University Faculty of Medicine, Department of Anesthesiology and Reanimation, Adana, Türkiye

ABSTRACT

Pediatric anesthesia requires careful consideration of fluid and electrolyte management due to the distinct physiological properties of children. Knowledge of postnatal adaptations is critical in avoiding complications from dehydration or overhydration. Children have a higher percentage of total body water, which makes them more vulnerable to imbalances in fluids. Insensible losses depend on respiratory rates and environmental conditions; otherwise, loss would result in dehydration if not corrected promptly. The neonatal renal physiology affects the filtration of fluids and the management of electrolytes, thus requiring individualized fluid therapy for neonates. Hormonal control, crossed capillary hydrodynamics, metabolic factors, and electrolyte equilibrium complicate pediatric fluid therapy further. Clinical evaluation measures aided by high-tech monitoring and multimodal methods will help assess children's fluid status. Isotonic solutions with adequate electrolyte composition are to be used as pediatric intravenous fluid therapy according to the recent guidelines. Crystalloids are preferred over colloids in the initial management of most pediatric patients. Recent evidence supports the use of isotonic balanced crystalloids to minimize iatrogenic complications such as hyponatremia and hyperchloremic acidosis, with ongoing monitoring tailored to individual patient needs.
Keywords: Anesthesia, fluid therapy, ıntravenous ınfusions, pediatrics, perioperative care.

ÖZET

Pediatrik anestezi, çocukların farklı fizyolojik özellikleri nedeniyle sıvı ve elektrolit yönetiminin dikkatle değerlendirilmesini gerektirir. Doğum sonrası adaptasyonların bilinmesi, dehidrasyon veya aşırı hidrasyondan kaynaklanan komplikasyonların önlenmesinde kritik öneme sahiptir. Çocukların toplam vücut suyu yüzdesi daha yüksektir, bu da onları sıvı dengesizliklerine karşı daha savunmasız hale getirir. Hissedilmeyen kayıplar solunum hızına ve çevresel koşullara bağlıdır; aksi takdirde, kayıp derhal düzeltilmezse dehidrasyona neden olur. Yenidoğan böbrek fizyolojisi sıvıların filtrasyonunu ve elektrolitlerin yönetimini etkiler, bu nedenle yenidoğanlar için bireyselleştirilmiş sıvı tedavisi gerektirir. Hormonal kontrol, kapiller hidrodinamik, metabolik faktörler ve elektrolit dengesi pediatrik sıvı tedavisini daha da karmaşık hale getirir. Yüksek teknolojili monitörizasyon ve multimodal yöntemlerle desteklenen klinik değerlendirme ölçütleri, çocukların sıvı durumunun değerlendirilmesine yardımcı olacaktır. Son kılavuzlara göre pediatrik intravenöz sıvı tedavisi olarak yeterli elektrolit bileşimine sahip izotonik solüsyonlar kullanılmalıdır. Çoğu pediatrik hastanın başlangıç yönetiminde kristalloidler kolloidlere tercih edilir, ancak sıvı yönetimi her bir hasta faktörüne göre uyarlanmalı ve perioperatif dönem boyunca sürekli izlenmelidir.
Anahtar kelimeler: Anestezi, sıvı tedavisi, intravenöz infüzyonlar, pediatri, perioperatif bakım.

Introduction

Perioperative fluid and electrolyte management is an essential component of pediatric anesthesia. The unique features of children's physiology, particularly their low reserve capacity and vulnerability to electrolyte imbalances, underscore the relevance of these issues to anesthesiologists. This article presents a review of the principles, problems, and evidence-based approaches to fluid and electrolyte management in pediatric surgical patients.

Pediatric intraoperative fluid management faces specific challenges due to their physiological traits, which are different from those of adults. which are high metabolic rates, high surface area to weight ratio, and immature renal function wherein all these factors significantly influence the fluid and electrolyte balance

Correspondence Address / Yazışma Adresi
Ersel Güleç, Cukurova University Faculty of Medicine, Department of Anesthesiology and Reanimation, Adana, Türkiye
e-mail: gulecersel@yahoo.com

2025;34(3):213-228
doi:10.17827/aktd.1667531
Geliş tarihi/ Received: 28.03.2025
Kabul tarihi/Accepted: 24.07.2025

during a surgical procedure. Such differences in physiology are key to the success of anesthesiologists in administering fluids and maintaining electrolyte balance in pediatric patients. Postnatal physiology changes dynamically and greatly impact the clinical strategy of managing fluid in newborns. These changes include adaptations of the total body water (TBW) shift and an evolving kidney function. It is of prime importance that these postnatal adaptations be understood, because from that understanding comes the opportunity to apply the most adequate therapy in avoiding either dehydration or fluid overload complications. The next sections will describe these physiological changes and their practice-based implications.

Total Body Water Dynamics

The dynamics of TBW are core to neonatal fluid therapy. TBW serves as a key indicator of hydration status in neonates, directly influencing their fluid requirements. Preterm neonates have increased TBW because their skin barriers are not fully developed and their renal systems are too immature; they are more in the range of 80-90% of their body weight versus 75% for term neonates[1]. This higher TBW makes them very labile concerning fluids, which necessitates very slow and careful titration of fluid intake to avoid either overload or dehydration. The extracellular (ECF) and intracellular fluid (ICF) distribution changes markedly with age. Preterm infants may have up to almost 80% of the TBW as extracellular, decreasing to about 60% by six months of age[2]. The fall in fluid as the child grows predominantly falls within the extracellular compartment and thus leads to the gradual hike of the ECF to ICF ratio until it approaches the adult ratio of 1:2 between the ages of about one and three years[1]. Younger children, with a higher proportion of ECF, pose greater challenges for anesthesiologists due to their altered responses to fluid administration and loss. On average, a 9-year-old child weighing 30 kg possesses about 60% of their body weight as TBW with ICF and ECF accounting for roughly 50% each. On the other hand, a neonate aged one month and weighing 4.5 kg possesses around 70% of their body weight as TBW with ICF constituting two-thirds and ECF one-third of TBW[1]. The TBW distribution by age is summarized in Figure 1. Such variations are important for fluid management, as they affect the volumes of fluids that need to be administered and the ease of redistribution of fluids between compartments throughout the perioperative period. Adults and children may use similar electrolyte-rich fluids if the renal function is adequate because the composition of ECF (plasma inclusive) is relatively constant across age groups[1]. The higher percentage of ECF to total body weight in younger children makes them much more vulnerable to dehydration and fluid imbalance than adults. Elevated vulnerability must be taken into account when evaluating fluid requirements and the probable effects of starvation as well as surgical stress on fluid balance in young children.

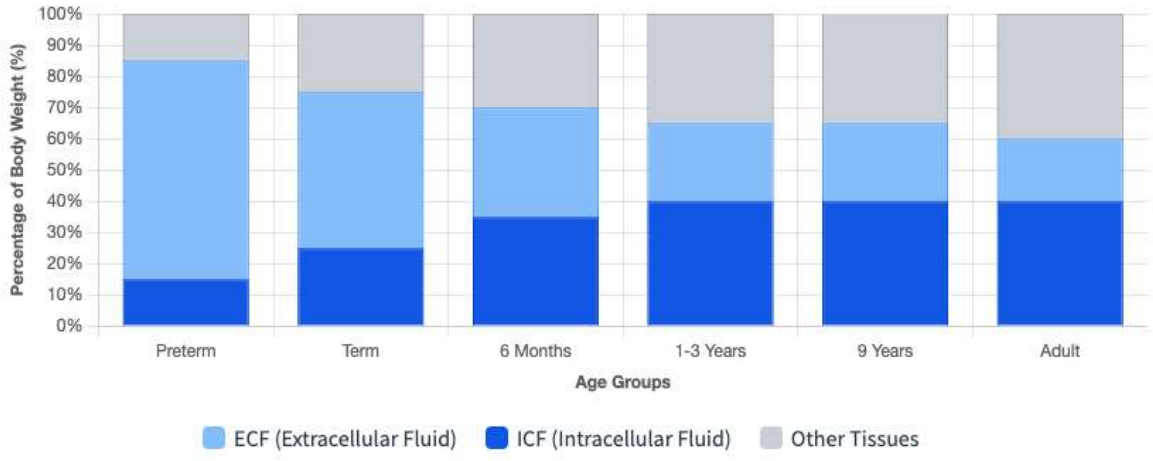


Figure 1. Age-related total body water distribution.

Insensible Water Losses

Compared to adults, children have a relatively larger body surface area in relation to weight, heightened insensible water loss mainly due to the respiratory system and the skin, and hence have increased fluid

requirements with a higher tendency for dehydration. The greater part of insensible water losses is through the lungs and skin in infants and younger children[2]. Neonates and particularly preterm neonates have very high insensible losses, which can account for a considerable percentage of their total water needs and, if not rapidly corrected, may lead to dehydration. The respiratory rate in children is also higher; therefore, there is an increase in insensible water loss by the respiratory route. These can become very high, particularly during mechanical ventilation with dry gases in the operating room. While present-day anesthesia machines are now available with humidification capabilities, the contribution of respiratory water loss should still be considered, especially in prolonged procedures or in pediatric patients with respiratory pathology that warrant elevated minute ventilation. Environmental factors in the operating room, such as temperature, humidity, and active warming devices, significantly affect insensible water loss in pediatric patients. High ambient temperatures and adequate levels of humidity can decrease these losses, and unreasonably dry or cooler conditions require the fluid to reach an even higher level. All these factors are to be taken into consideration by an anesthesiologist in developing a fluid management plan for pediatric patients, particularly neonates and infants because of the incomplete mechanism for temperature regulation at their age.

Renal Physiology and Development

The development of renal function is very important during infancy and early childhood because it plays a role in the regulation of fluid and electrolytes. The glomerular filtration rate (GFR) in full-term newborns is substantially less than adult levels and does not reach adult values until approximately one year of age[3]. The reduced filtrate delivery is related to the smaller surface area of capillaries for filtration, low systemic arterial pressure, and high resistance of the renal vasculature. Therefore, there is a low ultrafiltration pressure. The kidneys at birth have limited capacity to reabsorb water, with maximal urinary dilution being only 600 mOsm/kgH_2O as against 1200 mOsm/kgH_2O in adults. The decreased ability to concentrate urine is due to the hypotonic environment of the renal medulla and decreased response to antidiuretic hormone (ADH). Consequently, in neonates and young children, the ability to preserve water in states of deprivation or when there is increased loss of fluids is diminished. This makes them particularly at risk to the development of dehydration during the period of preoperative fasting. Tubular function develops slowly in early life. The reduced GFR in neonates not only impacts their filtration capacity but also has implications for electrolyte management, notably sodium. Newborns can have a high sodium excretion in the urine because the proximal tubule does not have a sufficient capacity to reabsorb sodium. Postnatally enhanced activity of the renin-angiotensin-aldosterone system increases distal tubular sodium reabsorption, which may decrease or not allow the excretion of substantial or rapid sodium loads. In this contradictory interplay between potential sodium loss and retention, the choice of maintenance fluid formulation should be taken with caution.

After surgery, the ability of newborns and young infants to balance acid and base in the body, which is crucial for their overall health, is influenced by how fluids are managed and the stress of surgery. The deficiency of hydrogen ion excretion and bicarbonate-generating capabilities place these patients at high risk of metabolic acidosis, particularly when there is inadequate tissue perfusion or increased metabolic needs and if large volumes of chloride-rich fluid are given, this may result in hyperchloremic metabolic acidosis of a severity that cannot be well-tolerated by infants due to their limited compensatory mechanisms.

Preterm neonates are structurally immature in terms of renal function. Postnatal diuresis, a normal phenomenon in newborns though very frequent in preterm neonates, is the outflow of excessive ECF and does not represent pathological fluid loss.

Recognition of such physiological processes is important to avoid unnecessary fluid input which can cause fluid overload with attendant consequences.

Hormonal Regulation of Fluid Balance

The important consequences of variations in hormonal control of fluid balance between children and adult populations are related to fluid management in the perioperative environment. More susceptible to several perioperative stresses in children, arginine vasopressin (AVP), another name for ADH, is essential for fluid

balance control. Following birth, serum ADH concentrations elevate and may rise significantly due to stressors such as surgical interventions, pain, nausea, and hypovolemia.

Increased ADH response in children during surgery can lead to temporary challenges in excreting free water, raising the risk of fluid retention and dilutional hyponatremia. This is quite important while evaluating perioperative fluid maintenance. Although hypotonic fluids were formerly used depending on metabolic demands, the awareness of non-osmotic ADH triggers in the perioperative phase has resulted in a movement towards isotonic solutions.

During the first week of newborn life, the renin-angiotensin-aldosterone system shows notable activity which raises aldosterone levels and causes more vascular tone[4]. These raised aldosterone levels improve the reabsorption of sodium in the distal tubules, therefore perhaps compromising the capacity to excrete significant or acute sodium loads. While it affects the responsiveness to fluid and electrolyte therapies, this higher aldosterone activity helps newborns to preserve blood pressure and vascular tone.

Atrial natriuretic peptide (ANP) is involved in the regulation of fluid balance in children, especially during instances of volume expansion. ANP facilitates natriuresis and diuresis, which helps to mitigate the sodium-retaining actions of the renin-angiotensin-aldosterone system[5]. Nonetheless, the functionality of this system may be underdeveloped in neonates and young infants, which could restrict their capacity to effectively manage volume expansion.

Exchanged Transcapillary Fluid

The Starling hypothesis describes transcapillary fluid exchange for both children and adults, with the equation detailing how pressure gradients affect fluid flow across capillary walls. Typically, fluid filtration at capillary arterial ends balances with reabsorption at venous ends. In children, increased capillary permeability in neonates and infants can lead to more fluid and protein moving into the interstitial space. Increased permeability can contribute to edema, especially in inflammatory diseases or with high-volume fluid infusion. Neonates and sick children often have low plasma oncotic pressure, primarily dependent on plasma proteins such as albumin[6]. Hypoalbuminemia is common in sick neonates, leading to fluid redistribution and edema formation. Diminished albumin synthesis due to hepatic immaturity further exacerbates oncotic pressure changes and fluid redistribution[7].

The glycocalyx is crucial for regulating blood vessel permeability and is a carbohydrate layer covering the vascular endothelium. Its development and changes over time due to human growth have been detailed. Although studies on the growth of the child's glycocalyx are scarce, it is assumed that its functional maturity enhances liquid transport, especially during stress from surgery or severe illness, evident by increased crystalloid solutions over 40-60 mL/kg[8, 9]. This could hinder isotonic fluid resuscitation in maintaining plasma volume and correcting fluid deficits. In children, lower thresholds may arise due to their unique physiologies, requiring more cautious resuscitation. Guidelines suggest colloid solutions as a second-line therapy after crystalloids, but the evidence is insufficient for definitive guidance[10]. Benefits should be considered alongside risks like allergic reactions, coagulopathy, and renal dysfunction with older hydroxyethyl starch (HES) solutions[11].

Acid-Base Assessment

Acid-base homeostasis is difficult to sustain in children owing to the fact that their metabolic rate is high but compensatory abilities are very low. The neonatal bicarbonate buffering system has a baseline concentration much lower at 20-22 mEq/L while in adults that level is more in the range of 24-26 mEq/L[12]. Thus, the low buffering capacity of neonates for metabolic acids decreases. Another factor that further lowers the low ability to buffer metabolic acids of neonates is the immature renal mechanism for the excretion of acids, which makes neonates much more susceptible to metabolic acidosis beyond stress conditions like surgery and critical illness.

IV fluid administration greatly affects acid-base balance. A major player in such a situation is Normal Saline (0.9% NaCl). As the most typical crystalloid solution, it carries 154 mmol/L chloride where the normal plasma level might average about 100-110 mmol/L[13]. Large normal saline loads may result in

hyperchloremic metabolic acidosis and dramatically worsen pre-existing acidosis in critically ill pediatric patients or patients involved in major surgical management requiring massive fluid input[8].

Some balanced crystalloids (BCS) that do not generate hyperchloremic acidosis and contain electrolyte composition like plasma, plus buffers such as lactate, acetate, or gluconate which are converted to bicarbonate in the body include Ringer's lactate and Plasma-Lyte[9]. These types of solutions are low potential mediators of iatrogenic acid-base disturbances and are gradually becoming the standard practice for intraoperative fluid therapy in the pediatric population to whom large volumes of fluids need to be administered[10]. Conditions that influence the relationship between perioperative fluid choice and acid-base balance are stronger in those with established renal or metabolic conditions. States of chronic kidney disease are associated with an acidosis, hyperkalemia, hypocalcemia, and hyperphosphatemia in a pediatric patient. Thus, during the intraoperative period fluids have to be chosen relative to any baseline electrolyte abnormality or acid-base abnormality to prevent further deviation during the time of surgery.

Glucose Homeostasis

Metabolic differences between children and adults are important in the regulatory control and pertinence of glucose to the regulation of the management of fluids during surgery. Neonates, particularly preterm neonates, have limited stores of glycogen and utilization of glucose accelerated, making them more prone to hypoglycemia in the fasted state[11]. The condition is even more deteriorated in a neonate who is inappropriate for gestational age, or intrauterine exposure to processes of maternal diabetes or beta-blockers[14-16].

Historically, many pediatricians have used glucose solutions as maintenance fluid therapy for pediatric patients due to a general feeling of hypoglycemia risk[17]. Surgical physiological stress leads to hyperglycemia because during any surgery, there is increased catecholamine stress with insulin resistance[18]. Osmotic diuresis can be expected resulting from hyperglycemia, leading to dehydration and adverse neurological outcomes due to electrolyte imbalances, especially in the settings of cerebral ischemia[19].

Modern strategies of glucose management have come to explicitly consider age, fasting duration, and the specific type of surgery. As patients are mostly children, undergoing elective surgeries that require only a short fasting period, routine glucose is usually not necessary at all. The neonates, infants <1 year, and children with a greater inherent risk of hypoglycemia would ideally benefit from treatment with 1–2% glucose in isotonic solutions, diabetic hyperglycemia being prevented very firmly while relatively safely removing the significant hyperglycemia risk[20].

Perioperative blood glucose monitoring remains relatively critical, more so when working with neonates, long surgical procedures, and high-risk patients who, if not carefully managed, may develop problems of glucose imbalance. Early diagnosis of derangements in glucose levels helps in timely intervention and modifications to fluid therapy. Although much debate continues on the optimal upper limit for safe blood glucose levels in children undergoing surgery, it is widely accepted that levels between 70 and 180 mg/dL would be appropriate[21].

The relationship of glucose to electrolyte balance should be appropriately recognized. Until quite recently, glucose used to be the standard maintenance fluid in a pediatric patient conjugated with hypotonic saline solutions i.e. 5% dextrose in either 0.2% NaCI or 0.45% NaCl. The realization that iatrogenic hyponatremia is a major complication of this practice has led to a recommendation that glucose be used only with isotonic solutions when absolutely necessary, and not with hypotonic fluids[22].

Electrolytes

Maintenance of electrolytes in children, inappropriate regulation, and relatively higher metabolic requirements presents some distinct challenges; since the regulatory mechanism is immature and metabolic requirements are high during this period of life.

Sodium is the major determinant of plasma osmolarity and, therefore, the control of the movement of fluid between the different compartments. Increased risk of hyponatremic brain edema in prepubescent children

results from a large brain-to-cranial-vault ratio, low Na-K ATPase activity, and high levels of ADH, especially under stress[23-25]. This relative increase in susceptibility mandates an increased surveillance role for the sodium solutions in IV fluids given in the context of pediatric anesthesia. This rising susceptibility suggests increased vigilance for sodium solutions within IV fluids in pediatric anesthesia management. Current evidence highly recommends isotonic solutions for maintenance therapy during the most common pediatric surgical conditions. Previous studies have additionally pointed to the possible association between hypotonic fluids and hyponatremia among the pediatric population[26]. In 2018, the American Academy of Pediatrics released a Key Action Statement recommending isotonic solutions with appropriate potassium chloride (KCl) and dextrose to be administered to pediatric patients 28 days to 18 years of age who require maintenance intravenous fluids[27].

The management of potassium levels in children is critically important, especially in the immediate postoperative period. Potassium chloride should be added to maintenance fluids unless nutritional fluid is contraindicated for the child because of hyperkalemia or deteriorating renal function[27]. There may be differences in opinions about the amount of potassium to be supplemented. However, in practice, most clinicians give 20 mEq/L of KCl to all patients irrespective of weight. Others suggest 10 mEq/L for patients under 10 kg [27]. Supplementation of potassium would be preferred in long procedures, to avoid hypokalemia, which can cause cardiac arrhythmia and neuromuscular weakness.

Clinical Assessment of Fluid Status

Current clinical and monitoring indicators impose limitations on the accurate assessment of fluid status and responsiveness in pediatric patients.

Traditional clinical markers of dehydration, such as skin turgor, mucous membrane moisture, and capillary refill, provide meaningful but sometimes slightly imprecise approximations to the state of hydration. The dependencies on these parameters are falling even lower in the conditions of anesthesia, that being driven by an influence on peripheral circulation, the effect of anesthetic agents on vascular tone, and external conditions regarding the ambient temperature and use of vasopressors.

Body weight changes remain fairly sensitive to relatively rapid changes in the fluid status of children. A reduction in weight specifically by at least 5% might point towards mild dehydration, 10% to moderate dehydration, and for 15% loss or higher, it would be severe dehydration- at risk of circulatory compromise. In emergent situations, however, practical application is often restricted due to the lack of available pre-illness weight.

Hemodynamic parameters include heart rate and blood pressure, pulse pressure but are of limited value in assessing volume status. Age and temperature, emotion, pain, anxiety, and age physiological variability in heart rate make it a relatively insensitive indicator of early hypovolemia in children[28]. Relatively late blood pressure is often maintained within normal ranges until relatively late in the progression of hypovolemia due to the compensatory increase in peripheral vascular resistance, particularly in healthy children with robust compensatory mechanisms.

Since there is limited information about responsiveness to fluids, Central Venous Pressure (CVP) monitoring is not used. The static values for CVP were also poorly correlated with intravascular volume and preload responsiveness. This complicates its interpretation due to shifts in venous compliance, intrathoracic pressure during mechanical ventilation, and cardiac function. In similar situations, it often creates a misleading perception of its actual presence[29-31].

Most parameters reflecting preload dependence are inspired by the functional interaction between the heart and lungs in mechanically ventilated patients—pulse pressure variation, stroke volume variation, and inferior vena caval respiratory variations. In adults, they have been studied extensively as predictors of fluid responsiveness[32, 33]. Evidence of their applicability in pediatric patients is poor and sometimes contradictory. This reduces the possibility of applying these dynamic indices clinically. Increased chest wall compliance and higher basal heart rate with smaller tidal volumes in children may further contribute to limited reliability of these dynamic parameters.

Technological advances, including esophageal Doppler monitoring, transpulmonary thermodilution, and non-invasive cardiac output monitoring, offer potential advantages in assessing fluid status and responsiveness in pediatrics. Table 2 summarizes various monitoring methods that can be used to assess fluid status in pediatric patients during the perioperative period. However, it tends to face challenges in terms of technological complexity as implementation factors, requiring expertise and, in general, insufficient validation in diverse cohorts of pediatrics studies.

The limitations of single assessment methods call for the need to undertake a multimodal approach to assess fluid status. Integrating clinical signs, basic hemodynamic data, laboratory parameters (lactate, base deficit, and urine output), and, if available, advanced monitoring tools enable one to achieve the most complete assessment of fluid status in a child and therefore guide proper management.

Table 2. Monitoring methods for body fluid status in pediatric perioperative care.

Monitoring Method	Key Characteristics	Advantages	Limitations
CLINICAL ASSESSMENT METHODS			
Clinical Signs	Heart rate, blood pressure, capillary refill time, mucous membrane moisture, skin turgor, mental status	Readily available Non-invasive First-line assessment tool	Late indicators Poor correlation with mild/moderate dehydration Subjective assessment
Body Weight	1 kg weight change approximates 1L fluid loss/gain	Gold standard for acute fluid changes Objective measurement	Baseline weights often unavailable in acute settings Affected by factors other than fluid (e.g., food intake)
Standardized Dehydration Assessment	Structured tools based on % weight loss and clinical symptoms	Categorizes dehydration severity Systematic approach	Relies on symptoms that may not always be present Variable interpretation between clinicians
INVASIVE HEMODYNAMIC MONITORING			
Central Venous Pressure	Direct measurement of right atrial pressure	Continuous monitoring Direct pressure measurement	Poor correlation with actual volume status Invasive with risks of central line Limited value in children
Arterial Pressure Monitoring	Continuous arterial pressure waveform analysis	Continuous hemodynamic data Enables dynamic parameter assessment	Limited predictive value in children Pulse pressure variation utility is variable Age/ventilation dependent
Esophageal Doppler Monitoring	EDM calculates SV, CO, FTc, and peak velocity. FTc serves as a preload indicator.	Minimally invasive Clinically accurate across all pediatric ages Continuous monitoring	Technical limitations such as age and size restrictions, probe positioning difficulties, and operator dependency Esophageal stricture, recent esophageal surgery, severe coagulopathy, and esophageal varices are absolute contraindications for EDM.
Transpulmonary Thermodilution (PiCCO)	Combines thermodilution with pulse contour analysis; measures CO, GEDV, EVLWI	Comprehensive hemodynamic data Useful in complex surgeries Validated in pediatric liver transplantation	Requires arterial and central venous access Not suitable for routine cases Invasive
NON-INVASIVE MONITORING TECHNOLOGIES			

Echocardiography & Ultrasound	Transthoracic echo, IVC ultrasound, lung ultrasound	Non-invasive Bedside evaluation Comprehensive cardiac assessment IVC collapsibility predicts fluid responsiveness	Operator-dependent Requires specialized training Intermittent measurement Equipment availability
Electrical Bioimpedance	Measures total body water, extracellular and intracellular fluid volumes	Non-invasive Validated in children Pre/post-op utility Good correlation with reference methods	Electromagnetic interference in OR Limited intraoperative monitoring Requires specific equipment
Electrical Cardiometry / USCOM	Non-invasive cardiac output monitoring based on changes in thoracic electrical conductivity / ultrasonic Doppler technology	Non-invasive Continuous monitoring Predicts fluid responsiveness Validated in children	Evidence still emerging Device-dependent results Variable accuracy in specific populations
Pleth Variability Index	Calculates respiratory variations in pulse oximetry waveforms	Non-invasive Can be automated Uses existing monitoring equipment	Limited value in spontaneously breathing children Variable evidence in children <2 years Requires mechanical ventilation for optimal use
EMERGING TECHNOLOGIES			
Near-Infrared Spectroscopy	Continuous monitoring of regional tissue oxygenation	Non-invasive Continuous monitoring Valued in cardiac surgery Reflects tissue perfusion	Limited to specialized settings Primarily research application Requires interpretation expertise
Advanced Ultrasound Techniques	Multi-organ protocols, left brachiocephalic vein assessment	Comprehensive assessment Non-invasive Point-of-care evaluation	Not standardized Requires operator skill Developing evidence base
Machine Learning Applications	Integrates multiple physiological variables for fluid responsiveness prediction	Multi-parameter integration Potential for improved accuracy Automated interpretation	Experimental Not in routine clinical use Requires validation

Abbreviations: CO, Cardiac Output; EDM, Esophageal Doppler Monitoring; EVLWI, Extravascular Lung Water Index; FTc, Corrected Flow Time; GEDV, Global End-Diastolic Volume; IVC, Inferior Vena Cava; SV, Stroke Volume; USCOM, Ultrasonic Cardiac Output Monitor.

Types of Fluids Used in Pediatric Intraoperative Management

Optimal intraoperative fluid treatments in pediatrics are performed using an IV route. Many IV fluids are available with major differences in properties, indications, and contraindications (see, Table 1). A detailed choice of fluid will assure patient-tailored administration that fits the needs of the patient, complies with the intricacies of the surgery performed on the patient, and complies with various physiological factors. The management of fluids in pediatrics has undergone considerable changes over the last decade. There is a

growing body of evidence to support these changes because it decreases iatrogenic complication risks as an evidence-based practice.

Table 1. Comparison of perioperative fluids in pediatric patients.

Fluid Type	Composition (per 100 mL)	Tonicity	Key Indications	Potential Adverse Effects & Considerations
CRYSTALLOIDS				
0.9% Sodium Chloride	Na^+ 15.4 mEq, Cl^- 15.4 mEq	Isotonic (308 mOsm/L)	Initial resuscitation for hypovolemia, replace gastric losses, correct hyponatremia and hypochloremia.	Large volumes may cause transient hyperchloremic metabolic acidosis and decreased glomerular filtration rate.
Lactated Ringer's Solution	Na^+ 13 mEq, K^+ 0.4 mEq, Ca^{2+} 0.3 mEq, Cl^- 10.9 mEq, Lactate 2.8 mEq	Isotonic (273 mOsm/L)	Maintenance fluid. Replacement of fluid deficits and ongoing losses. Balanced composition mimics plasma.	Lactate converts to bicarbonate; use cautiously in liver failure. Avoid with blood products due to calcium (clotting risk).
Plasma-Lyte A	Na^+ 14 mEq, K^+ 0.5 mEq, Mg^{2+} 0.3 mEq, Cl^- 9.8 mEq, Acetate 2.7 mEq, Gluconate 2.3 mEq	Isotonic (294 mOsm/L)	Maintenance fluid. Replacement of fluid deficits and ongoing losses. A balanced, buffered solution.	Contains magnesium, important for patients with renal failure. Acetate, metabolized by muscle, is suitable for liver dysfunction.
D5W	Dextrose 5g	Isotonic in the bag (252 mOsm/L), but physiologically hypotonic	Correction of free water deficit. Vehicle for medication administration.	Not suitable for resuscitation or maintenance as it spreads throughout body water compartments, providing minimal blood volume increase. Rapid dextrose metabolism leaves free water, raising the risk of hyponatremia and cerebral edema.
D5 ½ NS	Dextrose 5g, Na^+ 7.7 mEq, Cl^- 7.7 mEq	Hypertonic in the bag (406 mOsm/L), but physiologically hypotonic	Historically used for maintenance, but now less favored due to hypotonicity.	Poses a high risk of hyponatremia post-surgery due to elevated ADH levels; not advised for routine maintenance by current guidelines.
D5 ¼ NS	Dextrose 5g, Na^+ 3.4 mEq, Cl^- 3.4 mEq	Isotonic in the bag (280 mOsm/L), but physiologically hypotonic	Previously used for maintenance in neonates and young infants.	High risk of iatrogenic hyponatremia; isotonic solutions are preferred.
COLLOIDS				
5% Albumin	Albumin 5g	Isotonic	Volume expansion in severe hypovolemia or hypoalbuminemia. Cases with significant capillary leak.	Expensive. Risk of allergic reactions. No proven mortality benefit over crystalloids in most situations.

HES	Varies by product	Isotonic to hypertonic	Previously used for volume resuscitation.	Avoided in critically ill adults due to risks of kidney injury, coagulopathy, and increased mortality. Restricted and not recommended for children. Considered for surgeries with major bleeding risk, but evidence is lacking.
Gelatins	Varies by product	Isotonic	Volume expansion.	More anaphylactoid reactions than other colloids; shorter intravascular half-life than HES.

Abbreviations: ADH, Antidiuretic hormone; D5W, 5% Dextrose in Water; D5 ½ NS, 5% Dextrose+0.45% Sodium Chloride; D5 ¼ NS, 5% Dextrose+ 0.2% Sodium Chloride; HES, Hydroxyethyl Starches.

Crystalloid Solutions

Crystalloids play a rudimentary role in pediatric intraoperative fluid management, with major strides in their preparation and application over the years. Solutions consist primarily of a solvent with some electrolytes, which is notable for the lack of larger macromolecules of protein or starch. Tonicity classification describes isotonic and hypotonic solutions, whereas electrolyte composition may be categorized as balanced or unbalanced. Each type has its advantages and aspects to be taken into consideration, which are applied to pediatric patients based on the proper clinical setting.

Isotonic versus Hypotonic Solutions

Given the vulnerability of pediatric patients to electrolyte imbalances, isotonic solutions are preferred because they closely mimic the osmolarity of the child's plasma, reducing the risk of exacerbating imbalances. A major shift has occurred in pediatric fluid management, specifically in the fluid's tonicity for maintenance purposes. Traditionally, besides 5% glucose, hypotonic solutions were widely used, such as 0.2% NaCl (30 mmol/L sodium) and 0.45% NaCl (77 mmol/L sodium)[34]. Based on the historical framework established by Holliday and Segar, the metabolic needs of children are prescribed[35]. This methodology has been around since the 1950s and was really based on a wrong assumption, that relatively immature renal function of children would limit their ability to excrete sodium effectively. Moreover, contemporary research has proved that using hypotonic solutions radically increases potential risks for iatrogenic hyponatremia, especially in a perioperative setting[36].

The risks of hypotonic solutions have been extensively reported by several randomized controlled trials about the risks associated with the administration of hypotonic fluids to surgical patients. An interesting Cochrane review proved that there was a decrease in the incidence of hyponatremia by 52% when isotonic fluids were used as compared to hypotonic fluids[37]. The finding is of substantive relevance since in the prepubertal child, a very high degree of vulnerability to the cerebral edema phenomenon associated with hyponatremia is expressed, which includes increased brain-to-cranial-volume ratio, Na-K ATPase pump activity, and levels of ADH responsive to surgical stress. Hyponatremia can be a very significant clinical entity with restlessness, headache, seizures, and even sudden death in its severe form in this population[38, 39].

In its revised guidelines, the American Academy of Pediatrics now defines that isotonic solutions with proper concentrations of potassium chloride and dextrose be used for children aged from twenty-eight days to eighteen years for maintenance intravenous fluid therapy[22]. This dramatic reversal of advice marks a major deviation from customary practice, supported by newly available strong evidence towards the same end, which is the improvement of patient safety.

Balanced versus Unbalanced Solutions

In the field of isotonic solutions, one major comparison that can be formed is BCS against their unbalanced siblings, with the main characteristic being the widely used `normal saline' or 0.9% sodium chloride. Although it is very common in clinical practice, that solution does not meet the physiological standard

because the chloride level (154 mmol/L) is way over the level found in plasma, which is around at about 100-110 mmol/L.

The infusion of large amounts of 0.9% NaCl is associated with a diversity of adverse physiological effects. Such include hyperchloremic metabolic acidosis, fluid retention, renal vasoconstriction, and a fall in the GFR that have been seen both in adults and in pediatrics[40].

These formulations, indeed like BCS, have an electrolyte composition closer to that of human plasma and have buffering agents like lactate, acetate, or gluconate that are metabolized to bicarbonate. Such buffers decrease the appearance of hyperchloremic as well as dilutional metabolic acidosis, which can develop after infusion with normal saline. Some of the frequently used balanced solutions are Ringer's lactate (also known as Hartmann's solution) and Plasma-Lyte as well as other acetate buffered isotonic preparations.

A recent meta-analysis of three randomized controlled trials on 162 critically ill pediatric patients showed that hydration with balanced crystalloids improved metabolic acidosis and bicarbonate levels as compared with 0.9% NaCl at 4-12 hours[41]. In its recommendation, the Society of Pediatric and Neonatal Intensive Care also strongly prefers balanced crystalloid solutions as maintenance fluids in acutely and critically ill children[42]. In fact, in the European Consensus Statement from 2011 and the guidelines of the Association of the Scientific Medical Societies in Germany from 2016, preferential use of balanced crystalloid solutions for pediatric intraoperative maintenance fluid therapy is strongly advised[20, 43].

Solutions Containing Glucose

The shift from conventional fluid regimens to the use of glucose marks a radical change in the field of medicine. Pediatric patients, especially neonates and young infants, maintain pronounced biochemical differences in glucose metabolism compared with adults. With lower glycogen storage and higher basal glucose consumption rates, these individuals are prone to hypoglycemia in fasting states. Generally, 5% dextrose solutions previously served as maintenance infusions in pediatric care.

The surgical stimulation of the stress response also generally increases blood glucose levels by eliciting an increase in catecholamine secretion and developing insulin resistance[44-46]. Either condition can further worsen hyperglycemia admitted with high-concentration glucose solutions. This then makes the healthcare provider face a somewhat intense task in which they must mitigate the neurological hazards posed by both hyper- and hypoglycemia, the latter whose adverse effects might impend onto pediatric patients.

The current evidence suggests that in most pediatric patients, it is preferable to use isotonic balanced solutions with 1%-2.5% glucose than the previously used 5% glucose concentration[47, 48].

A 2-4% glucose solution administered at 10 ml/kg/h was found to be more effective in the prevention of intraoperative catabolism, insulin resistance, rebound hyperglycemia, and acidosis when compared with a 1% solution in low-birth-weight neonates[49]. This underlines the need for the right person and situation regarding the concentration of glucose. In the absence of other concerns, healthy children undergoing brief procedures for which they have been minimally fasted probably do not require provision of glucose[50]. Routine blood glucose measurements are, however, imperative for neonates, individuals undergoing prolonged procedures, and those with imbalances risk factors.

Colloid Solutions

Colloids comprise relatively large molecules, mostly proteins and starches. Logically, these substances should be kept inside the intravascular compartment for a longer time than crystalloids. Therefore, theoretically, colloids should be more effective in expanding volume. However, the debate concerning the use of colloids in pediatrics still continues because relatively low-quality evidence does not yet provide an answer that would be sufficiently satisfactory for guiding patient management[51]. Colloids can be primarily structured as natural proteins and synthetic colloids.

Natural Protein Colloids

Albumin has usually been taken as the gold standard colloid for pediatric patients. However, new evidence has complicated that old perspective. In the year 2023, a quality improvement initiative implemented a systematic change program intervention to reduce the use of 5% human albumin solution in the Pediatric Intensive Care Unit[52]. Human albumin comes in concentrations from 5% to 20%, with 5%, the osmotic equivalent to plasma[53]. More than 50% of total plasma protein, and in fact, 80% of intravascular oncotic pressure, is due to this protein[54].

Although the empirical promise of albumin may appear optimistic, the evidence that is currently available does not support its clinical superiority over crystalloids. The use of albumin has been extensively researched among critically ill adult populations, and no study has shown a significant reduction in mortality[55, 56]. Furthermore, high-quality studies involving pediatric populations are few. Although it is known to be the least allergenic colloidal solution, the disadvantage of albumin is that it is the most expensive treatment with the potential to leave the blood vessels for the extra-vascular space, especially with high vascular permeability due to inflammation and critical illness conditions. Other natural protein colloids include stable human serum and lyophilized plasma; however, their use is uncommon, and evidence to support their use in pediatric perioperative settings is lacking.

Synthetic Colloids

Synthetic colloids have emerged because of their high cost and limited availability of albumin. The major classes are HES, gelatin, and dextran, which differ in their properties and safety considerations. Development in the third-generation HES solutions such as tetrastarch (HES 130/0.4) is the definitive response to the prolonged evolution observed. This is inspired mainly by the goal to rectify security issues attached to the former mixture Contemporary starches with a low molecular mass of 130,000 Da makes them safer. Hence, the risk of associated adverse events, such as renal failure, itching, and changes in hemostasis, is lower, while their volumetric effects are about the same[57].

A meta-analysis of nine randomized controlled trials showed that third-generation HES administration did not affect renal output or blood loss in pediatric consented patients to surgery[58]. There is reason to believe that HES in balanced electrolyte solutions may have less effect on acid-base and electrolyte balance compared to HES in saline[59].

With reference to their influence on coagulation and renal function, the questions about the synthetic colloids remain to be debated[60, 61]. Different studies have proposed increased blood loss potential after pediatric cardiopulmonary bypass procedures when HES solutions are used, though this is not constantly associated with higher transfusion needs[62, 63]. Some data is available on the "tipping of the balance" of thromboelastographic alterations in pediatric samples towards HES[64].

Gelatin solutions have high potential for eliciting anaphylactoid reactions and little positive volume effects, almost no hemostasis impact[65, 66]. Dextrans, being less used today, impede coagulation and pose imminent risks of anaphylaxis[67, 68].

Regulatory issues have played a major role in the availability of synthetic colloids, with HES products having been placed under regulatory suspension for patients of all ages in both Europe and the United States. This situation is further constraining the selection available to pediatric anesthesiologists.

Clinical Application and Limitations

The function of colloids in pediatric patient fluid balance management continues to evolve. However, current recommendations support the preference for crystalloids as the initial therapy[69]. However, there are situations where colloids may be quite appropriate, when, first of all, crystalloids are not effective. Some guidelines suggest starting colloids after 30-50 ml/kg of crystalloids have been given without achieving successful volume restoration. Most institutions have limited the routine use of colloids because they are more expensive than crystalloids and have scarce supporting evidence of improved outcomes.

A pragmatic approach, therefore, is that balanced crystalloid solutions should be used first, and colloids should be reserved for specific indications. Blood products should only be used when Hb levels or coagulation parameters indicate need. In scenarios where colloids are thought necessary, third-generation HES solutions might provide such a compromise amongst efficacy and safety in children with normal renal function and coagulation, although this remains controversial. There remains even more specific caution about synthetic colloids in neonates (due to immature coagulation systems) and post-cardiopulmonary bypass procedures.

Conclusion

Fluid management in pediatric surgery requires attention to total body fluid physiology, individual circumstances, and current evidence. The use of isotonic balanced crystalloid solutions with glucose (1% to 2.5%) is strongly advocated, moving away from previous hypotonic solutions with higher glucose levels. Evidence is limited in more controversial areas such as the use of colloids or advanced monitoring techniques. Colloids have limited roles, and crystalloids are preferred as first-line therapy. Colloid therapy may be beneficial in high blood loss surgeries (e.g., cardiac surgery, major tumor surgeries, major trauma) where crystalloid administration exceeds 30-50 mL/kg without hemodynamic stability. Caution is advised in neonates and preterm infants due to risks of adverse effects. Colloids should be avoided in patients with renal dysfunction or coagulopathy. While HES solution has mixed safety profiles, natural colloids like albumin may be considered in specific cases, despite limited evidence for improved outcomes.

Pediatric fluid management must be age-appropriate. Neonates require tailored approaches, whereas school-age children typically tolerate standard isotonic protocols, with adolescents needing more adult-like strategies. Crucial gaps in pediatric fluid therapy include validating dynamic fluid responsiveness monitors in children and developing pediatric-specific assessment protocols for point-of-care ultrasound. The application of artificial intelligence in fluid management, including predictive algorithms for fluid responsiveness, is an emerging area of interest. Comparative effectiveness research is needed for optimal fluid strategies in subpopulations with conditions such as congenital heart disease and chronic kidney disease. Advancements in pediatric fluid monitoring should prioritize non-invasive, continuous tools tailored for children. Wearable devices for real-time fluid status assessment and automated decision support systems could enhance fluid management. Additionally, integrating telemedicine for remote monitoring in varied healthcare settings may improve pediatric outcomes.

In summary, while crystalloid solutions are central to pediatric intraoperative fluid therapy, individual treatment strategies based on age and surgical complexity are crucial. Future research should focus on pediatric-specific technologies, validating fluid parameters, and refining evidence-based protocols.

References

1. Lee H, Kim JT. Pediatric perioperative fluid management. Korean J Anesthesiol. 2023;76(6):519-30. doi:10.4097/kja.23128
2. Mathew A, Rai E. Pediatric perioperative fluid management. Saudi J Anaesth. 2021;15(4):435-40. doi:10.4103/sja.sja_140_21
3. Iacobelli S, Guignard JP. Maturation of glomerular filtration rate in neonates and infants: an overview. Pediatr Nephrol. 2021;36(6):1439-46. doi:10.1007/s00467-020-04632-1
4. Al Awad EH, Yusuf K, Soraisham AS, Obaid H, Sundaram A, Samedi V et al.. Transient Hyperaldosteronism and Neonatal Hypertension: Case Series and Literature Review. J Clin Neonatol. 2018;7(3):185-9. doi:10.4103/jcn.JCN_57_18
5. Rao S, Pena C, Shurmur S, Nugent K. Atrial Natriuretic Peptide: Structure, Function, and Physiological Effects: A Narrative Review. Curr Cardiol Rev. 2021;17(6):e051121191003. doi:10.2174/1573403X17666210202102210.
6. Weaver LJ, Travers CP, Ambalavanan N, Askenazi D. Neonatal fluid overload-ignorance is no longer bliss. Pediatr Nephrol. 2023;38(1):47-60. doi:10.1007/s00467-022-05514-4.
7. Bunt JE, Rietveld T, Schierbeek H, Wattimena JL, Zimmermann LJ, van Goudoever JB. Albumin synthesis in preterm infants on the first day of life studied with [1-13C]leucine. Am J Physiol Gastrointest Liver Physiol. 2007;292(4):G1157-61. doi:10.1152/ajpgi.00300.2006.
8. Stanski NL, Gist KM, Pickett K, Brinton JT, Sadlowski J, Wong HR, et al.. Electrolyte derangements in critically ill children receiving balanced versus unbalanced crystalloid fluid resuscitation. BMC Nephrol. 2022;23(1):388. doi:10.1186/s12882-022-03009-w.
9. Semler MW, Self WH, Rice TW. Balanced Crystalloids versus Saline in Critically Ill Adults. N Engl J Med. 2018;378(20):1951. doi:10.1056/NEJMc1804294.
10. Arya V, Kavitha M, Mittal K, Gehlawat VK. Plasmalyte versus normal saline as resuscitation fluid in children: A randomized controlled trial. Journal of Pediatric Critical Care. 2021;8(3):134-8. doi:10.4103/jpcc.jpcc_14_21.

11. Committee on F, Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011;127(3):575-9. doi:10.1542/peds.2010-3851.
12. Iacobelli S, Guignard JP. Renal aspects of metabolic acid-base disorders in neonates. Pediatr Nephrol. 2020;35(2):221-8. doi:10.1007/s00467-018-4142-9.
13. Ramanan M, Hammond N, Billot L, Delaney A, Devaux A, Finfer S et al.. Serum chloride concentration and outcomes in adults receiving intravenous fluid therapy with a balanced crystalloid solution or 0.9% sodium chloride. Intensive Care Med. 2025;51(2):249-58. doi:10.1007/s00134-024-07764-2.
14. Rasmussen AH, Wehberg S, Fenger-Groen J, Christesen HT. Retrospective evaluation of a national guideline to prevent neonatal hypoglycemia. Pediatr Neonatol. 2017;58(5):398-405. doi:10.1016/j.pedneo.2016.12.002.
15. Bateman BT, Patorno E, Desai RJ, Seely EW, Mogun H, Maeda A et al.. Late Pregnancy beta Blocker Exposure and Risks of Neonatal Hypoglycemia and Bradycardia. Pediatrics. 2016;138(3):e20160731. doi:10.1542/peds.2016-0731.
16. Leelanukrom R, Cunliffe M. Intraoperative fluid and glucose management in children. Paediatr Anaesth. 2000;10(4):353-9. doi:10.1046/j.1460-9592.2000.00536.x.
17. Becke K, Eich C, Hohne C, Johr M, Machotta A, Schreiber M et al.. Choosing Wisely in pediatric anesthesia: An interpretation from the German Scientific Working Group of Paediatric Anaesthesia (WAKKA). Paediatr Anaesth. 2018;28(7):588-96. doi:10.1111/pan.13383.
18. Floh AA, Manlhiot C, Redington AN, McCrindle BW, Clarizia NA, Caldarone CA, et al.. Insulin resistance and inflammation are a cause of hyperglycemia after pediatric cardiopulmonary bypass surgery. J Thorac Cardiovasc Surg. 2015;150(3):498-504 e1. doi:10.1016/j.jtcvs.2015.06.028.
19. Kostopoulou E, Sinopidis X, Fouzas S, Gkentzi D, Dassios T, Roupakias S et al.. Diabetic Ketoacidosis in Children and Adolescents; Diagnostic and Therapeutic Pitfalls. Diagnostics (Basel). 2023;13(15):2602. doi:10.3390/diagnostics13152602.
20. Sumpelmann R, Becke K, Crean P, Johr M, Lonnqvist PA, Strauss JM, et al.. European consensus statement for intraoperative fluid therapy in children. Eur J Anaesthesiol. 2011;28(9):637-9. doi:10.1097/EJA.0b013e3283446bb8.
21. de Bock M, Codner E, Craig ME, Huynh T, Maahs DM, Mahmud FH et al.. ISPAD Clinical Practice Consensus Guidelines 2022: Glycemic targets and glucose monitoring for children, adolescents, and young people with diabetes. Pediatr Diabetes. 2022;23(8):1270-6. doi:10.1111/pedi.13455.
22. Feld LG, Neuspiel DR, Foster BA, Leu MG, Garber MD, Austin K et al.. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. Pediatrics. 2018;142(6):e20183083. doi:10.1542/peds.2018-3083.
23. Ayus JC, Achinger SG, Arieff A. Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. Am J Physiol Renal Physiol. 2008;295(3):F619-24. doi:10.1152/ajprenal.00502.2007.
24. Oh GJ, Sutherland SM. Perioperative fluid management and postoperative hyponatremia in children. Pediatr Nephrol. 2016;31(1):53-60. doi:10.1007/s00467-015-3081-y.
25. Hill LL. Body composition, normal electrolyte concentrations, and the maintenance of normal volume, tonicity, and acid-base metabolism. Pediatr Clin North Am. 1990;37(2):241-56. doi:10.1016/s0031-3955(16)36865-1.
26. Eaddy N, Watene C. Perioperative management of fluids and electrolytes in children. BJA Educ. 2023;23(7):273-8. doi:10.1016/j.bjae.2023.03.006.
27. Kight BP, Waseem M. Pediatric Fluid Management. *StatPearls*. StatPearls Publishing Copyright © 2025, StatPearls Publishing LLC.; 2025..
28. Heal C, Harvey A, Brown S, Rowland AG, Roland D. The association between temperature, heart rate, and respiratory rate in children aged under 16 years attending urgent and emergency care settings. Eur J Emerg Med. 2022;29(6):413-6. doi:10.1097/MEJ.0000000000000951.
29. De Backer D, Vincent JL. Should we measure the central venous pressure to guide fluid management? Ten answers to 10 questions. Crit Care. 2018;22(1):43. doi:10.1186/s13054-018-1959-3.
30. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest. 2008;134(1):172-8. doi:10.1378/chest.07-2331.
31. Cecconi M, Aya HD. Central venous pressure cannot predict fluid-responsiveness. Evid Based Med. 2014;19(2):63. doi:10.1136/eb-2013-101496.
32. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002;121(6):2000-8. doi:10.1378/chest.121.6.2000.
33. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med. 2009;37(9):2642-7. doi:10.1097/CCM.0b013e3181a590da.
34. Costlow L. Maintenance Intravenous Fluids in Children: AAP Provides Recommendations. Am Fam Physician. 2019;100:251.
35. Holliday MA, Ray PE, Friedman AL. Fluid therapy for children: facts, fashions and questions. Arch Dis Child. 2007;92:546-50. doi:10.1136/adc.2006.106377.
36. Andersen C, Afshari A. Impact of perioperative hyponatremia in children: A narrative review. World J Crit Care Med. 2014;3(4):95-101. doi:10.5492/wjccm.v3.i4.95.
37. McNab S, Ware RS, Neville KA, Choong K, Coulthard MG, Duke T et al.. Isotonic versus hypotonic solutions for maintenance intravenous fluid administration in children. Cochrane Database Syst Rev. 2014;2014(12):CD009457. doi:10.1002/14651858.CD009457.pub2.
38. Sarnaik AP, Meert K, Hackbarth R, Fleischmann L. Management of hyponatremic seizures in children with hypertonic saline: a safe and effective strategy. Crit Care Med. 1991;19(6):758-62. doi:10.1097/00003246-199106000-00005.
39. Bezinover D, Nahouraii L, Sviatchenko A, Wang M, Kimatian S, Saner FH et al.. Hyponatremia Is Associated With Increased Mortality in Children on the Waiting List for Liver Transplantation. Transplant Direct. 2020;6(10):e604. doi:10.1097/txd.0000000000001050.

40. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. Ann Surg. 2012;256(1):18-24. doi:10.1097/SLA.0b013e318256be72.
41. Lehr AR, Rached-d'Astous S, Barrowman N, Tsampalieros A, Parker M, McIntyre L et al.. Balanced Versus Unbalanced Fluid in Critically Ill Children: Systematic Review and Meta-Analysis. Pediatr Crit Care Med. 2022;23(3):181-91. doi:10.1097/pcc.0000000000002890.
42. Brossier DW, Tume LN, Briant AR, Jotterand Chaparro C, Moullet C, Rooze S et al.. ESPNIC clinical practice guidelines: intravenous maintenance fluid therapy in acute and critically ill children- a systematic review and meta-analysis. Intensive Care Med. 2022;48(12):1691-708. doi:10.1007/s00134-022-06882-z.
43. Sumpelmann R, Becke K, Brenner S, Breschan C, Eich C, Hohne C et al.. Perioperative intravenous fluid therapy in children: guidelines from the Association of the Scientific Medical Societies in Germany. Paediatr Anaesth. 2017;27(1):10-8. doi:10.1111/pan.13007.
44. Finnerty CC, Mabvuure NT, Ali A, Kozar RA, Herndon DN. The surgically induced stress response. JPEN J Parenter Enteral Nutr. 2013;37(5):21-9. doi:10.1177/0148607113496117.
45. Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000;85(1):109-17. doi:10.1093/bja/85.1.109.
46. Yuki K, Matsunami E, Tazawa K, Wang W, DiNardo JA, Koutsogiannaki S. Pediatric Perioperative Stress Responses and Anesthesia. Transl Perioper Pain Med. 2017;2(1):1-12.
47. Lindestam U, Norberg Å, Frykholm P, Rooyackers O, Andersson A, Fläring U. Balanced electrolyte solution with 1% glucose as intraoperative maintenance fluid in infants: a prospective study of glucose, electrolyte, and acid-base homeostasis. Br J Anaesth. 2024;134(5):1432-9. doi:10.1016/j.bja.2024.08.041.
48. Sumpelmann R, Mader T, Eich C, Witt L, Osthaus WA. A novel isotonic-balanced electrolyte solution with 1% glucose for intraoperative fluid therapy in children: results of a prospective multicentre observational post-authorization safety study (PASS). Paediatr Anaesth. 2010;20(11):977-81. doi:10.1111/j.1460-9592.2010.03428.x.
49. Datta PK, Pawar DK, Baidya DK, Maitra S, Aravindan A, Srinivas M et al.. Dextrose-containing intraoperative fluid in neonates: a randomized controlled trial. Paediatr Anaesth. 2016;26(6):599-607. doi:10.1111/pan.12886.
50. Vetter L, Sümpelmann R, Rudolph D, Röher K, Vetter M, Boethig D et al.. Short anesthesia without intravenous fluid therapy in children: Results of a prospective non-interventional multicenter observational study. Paediatr Anaesth. 2024;34(5):454-8. doi:10.1111/pan.14847.
51. Bailey AG, McNaull PP, Jooste E, Tuchman JB. Perioperative crystalloid and colloid fluid management in children: where are we and how did we get here? Anesth Analg. 2010;110(2):375-90. doi:10.1213/ANE.0b013e3181b6b3b5.
52. Inata Y, Nakagami-Yamaguchi E, Hatachi T, Ito Y, Akamatsu T, Takeuchi M. Reducing Human Album Solution Use in the Pediatric Intensive Care Unit. Pediatr Qual Saf. 2023;8(4):e667. doi:10.1097/pq9.0000000000000667.
53. Zdolsek M, Hahn RG. Kinetics of 5% and 20% albumin: A controlled crossover trial in volunteers. Acta Anaesthesiol Scand. 2022;66(7):847-58. doi:10.1111/aas.14074.
54. Weil MH, Henning RJ, Puri VK. Colloid oncotic pressure: clinical significance. Crit Care Med. 1979;7(3):113-6. doi:10.1097/00003246-197903000-00006.
55. Zou Y, Ma K, Xiong J-B, Xi C-H, Deng X-J. Comparison of the effects of albumin and crystalloid on mortality among patients with septic shock: systematic review with meta-analysis and trial sequential analysis. Sao Paulo Med J. 2018;136(05):421-32. doi:10.1590/1516-3180.2017.0285281017.
56. Patel A, Laffan MA, Waheed U, Brett SJ. Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality. BMJ. 2014;349(22):g4561. doi:10.1136/bmj.g4561.
57. Piazza O, Scarpati G, Tufano R. Update on transfusion solutions during surgery: review of hydroxyethyl starches 130/0.4. Int J Gen Med. 2010;3:287-95. doi:10.2147/IJGM.S3495.
58. Thy M, Montmayeur J, Julien-Marsollier F, Michelet D, Brasher C, Dahmani S et al.. Safety and efficacy of peri-operative administration of hydroxyethyl starch in children undergoing surgery: A systematic review and meta-analysis. Eur J Anaesthesiol. 2018;35(7):484-95. doi:10.1097/EJA.0000000000000780.
59. Base E, Standl T, Mahl C, Jungheinrich C. Comparison of 6% HES 130/0.4 in a balanced electrolyte solution versus 6% HES 130/0.4 in saline solution in cardiac surgery. Crit Care. 2006;10(1):176. doi:10.1186/cc4523.
60. Myburgh JA, Finfer S, Bellomo R, Billot L, Cass A, Gattas D, et al.. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med. 2012;367(20):1901-11. doi:10.1056/NEJMoa1209759.
61. Hartog CS, Reuter D, Loesche W, Hofmann M, Reinhart K. Influence of hydroxyethyl starch (HES) 130/0.4 on hemostasis as measured by viscoelastic device analysis: a systematic review. Intensive Care Med. 2011;37:1725-37. doi:10.1007/s00134-011-2385-z.
62. Navickis RJ, Haynes GR, Wilkes MM. Effect of hydroxyethyl starch on bleeding after cardiopulmonary bypass: a meta-analysis of randomized trials. J Thorac Cardiovasc Surg. 2012;144(1):223-30. doi:10.1016/j.jtcvs.2012.04.009.
63. Van Der Linden P, James M, Mythen M, Weiskopf RB. Safety of modern starches used during surgery. Anesth Analg. 2013;116(1):35-48. doi:10.1213/ANE.0b013e31827175da.
64. Haas T, Preinreich A, Oswald E, Pajk W, Berger J, Kuehbacher G, et al.. Effects of albumin 5% and artificial colloids on clot formation in small infants. Anaesthesia. 2007;62(10):1000-7. doi:10.1111/j.1365-2044.2007.05186.x.
65. Saudan S. Is the use of colloids for fluid replacement harmless in children? Curr Opin Anaesthesiol. 2010;23(3):363-7. doi:10.1097/ACO.0b013e328339384e.
66. Thomas-Rueddel DO, Vlasakov V, Reinhart K, Jaeschke R, Rueddel H, Hutagalung R, et al.. Safety of gelatin for volume resuscitation--a systematic review and meta-analysis. Intensive Care Med. 2012;38(7):1134-42. doi:10.1007/s00134-012-2560.
67. Mitra S, Khandelwal P. Are All Colloids Same? How to Select the Right Colloid? Indian Journal of Anaesth. 2009;53:592-607.

68. Shiratori T, Sato A, Fukuzawa M, Kondo NI, Tanno S. Severe Dextran-Induced Anaphylactic Shock during Induction of Hypertension-Hypervolemia-Hemodilution Therapy following Subarachnoid Hemorrhage. Case Rep Crit Care. 2015;2015:967560. doi:10.1155/2015/967560.
69. Akech S, Ledermann H, Maitland K. Choice of fluids for resuscitation in children with severe infection and shock: systematic review. BMJ. 2010;341:c4416. doi:10.1136/bmj.c4416.

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Müller's Muscles: Three Different Smooth Muscles of the Eye and Orbit

Müller kasları: Göz ve Orbitanın Üç Farklı Düz Kası

Cansu Kibar Karagöz[1], Hatice Yenigül[1], Özge Coşkun Sağlam[2]

[1]Department of Anatomy, Faculty of Medicine, Istanbul Arel University, Istanbul, Türkiye
[2]Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Istanbul Bilgi University, Istanbul, Türkiye

ABSTRACT

Purpose: The eponym "Müller's muscle" has been used in various textbooks and academic articles to refer collectively to three different smooth muscles: orbital muscle, superior tarsal muscle and the circular fibers of the ciliary muscle. The aim of this review is to highlight the terminological confusion created in the literature by the use of the Müller's muscle eponym as a common name for three different muscles associated with the eye and orbit.

Methods: A comprehensive literature review was conducted in academic databases such as PubMed, Google Scholar, Scopus, and Web of Science to clarify clarify the appropriate usage of the term "Müller's muscle". Additionally, the descriptions of these muscles in leading medical school sources, atlases, and textbooks were examined. The detailed topographical locations, anatomical and morphological characteristics, histological structures, innervation and vascularisation, and clinical syndromes of the muscles were presented in a comparative manner.

Conclusion: We believe that our study will contribute to preventing naming confusion regarding these muscles, collectively referred to as 'Müller's muscle,' in future anatomy atlases, clinical guidebooks, and scientific studies.

Keywords: Müller's muscle, orbit, anatomy, eye

ÖZET

Amaç: "Müller kası" eponimi, çeşitli ders kitaplarında ve akademik makalelerde üç farklı düz kası (m. orbitalis, m. tarsalis superior ve m. ciliaris'in dairesel lifleri) ifade etmek için kullanılmıştır. Bu derlemenin amacı, literatürde Müller kası eponiminin göz ve orbita ile ilişkili üç farklı kas için ortak bir isim olarak kullanılmasıyla oluşan terminolojik karışıklığa dikkat çekmektir.

Yöntem: "Müller kası" teriminin uygun kullanımını netleştirmek için PubMed, Google Akademik, Scopus ve Web of Science gibi akademik veri tabanlarında kapsamlı bir literatür taraması yapıldı. Ayrıca, önde gelen tıp fakültesi kaynakları, atlaslar ve ders kitaplarındaki bu kasların tanımları incelendi. Kasların ayrıntılı topografik konumları, anatomik ve morfolojik özellikleri, histolojik yapıları, innervasyon ve vaskülarizasyonu ve klinik sendromları karşılaştırmalı olarak sunuldu.

Sonuç: Çalışmamızın, gelecekte anatomi atlaslarında, klinik rehberlerde ve bilimsel çalışmalarda topluca 'Müller kası' olarak adlandırılan bu kaslara ilişkin isimlendirme karışıklığının önlenmesine katkıda bulunacağına inanıyoruz.

Anahtar kelimeler: Müller kası, orbita, anatomi, göz

Introduction

The eponymous names of the three smooth muscles located in the orbit are attributed to the German anatomist Heinrich Müller. These muscles are: orbital muscle, superior tarsal muscle, and the ciliary muscle which are characterized by their circular fibers. The use of the term "Müller's muscle" to refer to all three muscles in the literature can lead to confusion. Therefore, a literature review was conducted using academic databases such as PubMed, Google Scholar, Scopus, and Web of Science in order to clarify the use of the term 'Müller's muscle'.

Correspondence Address / Yazışma Adresi
Cansu Kibar Karagöz, Istanbul Arel University, Faculty of Medicine Department of Anatomy, Istanbul, Türkiye e-mail: cansukibar7@gmail.com

2025;34(3):229-236
doi:10.17827/aktd.1612117
Geliş tarihi/ Received: 02.01.2025
Kabul tarihi/Accepted: 16.07.2025

This review will provide literature on these three muscles, all referred to as "Müller's muscles," and will discuss the use of the term "Müller's muscle."

Orbital Muscle

The orbital muscle of Müller is a small extraocular smooth muscle embedded in the periorbita[1]. It is located posteriorly in the orbit and fills the inferior orbital fissure. It separates the periorbital fat from the buccal fat pad[2]. It extends from the sphenoid bone to the zygomatic and maxillary bones and is closely related to the Zinn's ring (Common tendinous ring; Common anular tendon)[3] (Figure 1).

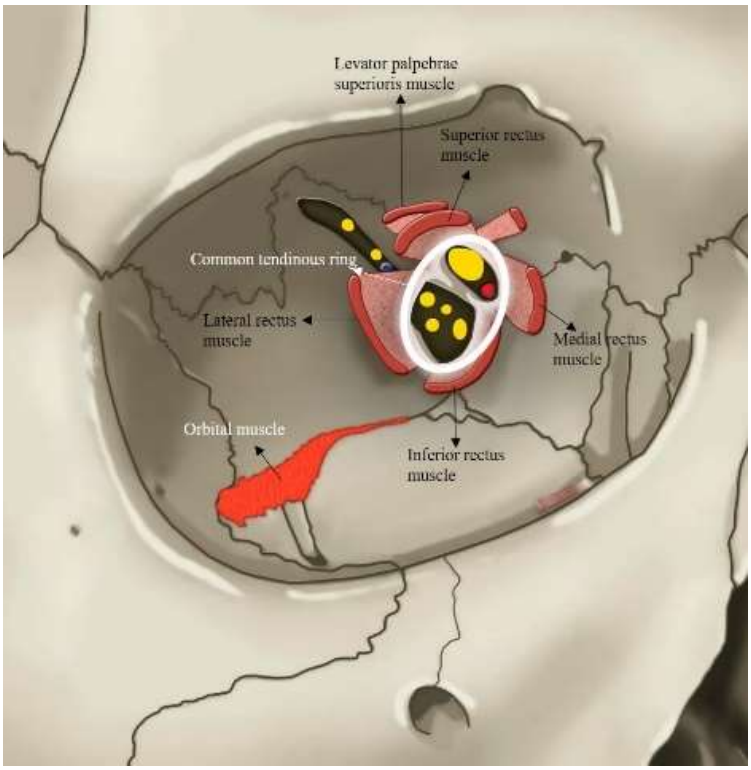


Figure 1. Muscles located in the right orbit, eye removed.

The superior surface of the muscle is adjacent to the rectus inferior muscle, the inferior branch of the oculomotor nerve, and the inferior ophthalmic vein. The inferior surface of the muscle is in proximity to the pterygopalatine fossa and the maxillary, zygomatic, and infraorbital nerves passing through this fossa[4].

The body of the muscle is wider than the inferior orbital fissure. The orbital muscle attaches laterally to the inferior orbital fissure on the ventral side and medially to the inferior orbital fissure on the dorsal side. The average weight of the muscle is 0.22 ± 0.19 g, with an average width of 4 ± 1 mm at its widest point and an average length of 22 ± 5 mm[3].

Sappey defined the orbital muscle as the "lower orbital muscle," while Whitnall referred to it as the "periorbital muscle"[5].

The orbital muscle is composed of smooth muscle cells. The muscle fibers extend from the craniomedial to the caudolateral direction in a slightly oblique plane towards the apex of the orbit. The muscle is largely made up of bundles of fibers that run parallel to each other. The dorsomedial portion of these parallel fibers is complemented and reinforced by vertically oriented muscle fibers[6]. Blood vessels and nerves, including the inferior ophthalmic vein, infraorbital artery, infraorbital nerve, and zygomatic nerve, pass between the muscle fibers[3]. Sympathetic innervation is provided by the superior cervical ganglion via the internal carotid plexus[7].

Its function in humans is not well understood. During embryonic development, it forms approximately 50% of the orbital base[8] and is thought to isolate the orbital contents from surrounding tissues[9]. Additionally,

since it is pierced by veins connecting the ophthalmic veins to the pterygoid plexus, it is believed to play a role in regulating venous blood flow[10]. In adults, contraction of this muscle may cause a slight protrusion of the eye globe[7]. Furthermore, it serves as a septum for structures within the orbit, which is crucial for the normal development of extraocular structures[9].

Due to its location covering the inferior orbital fissure, this muscle has clinical and surgical significance as it provides a medical intervention to the orbit[4]. If sympathetic innervation to the orbital muscle is impaired, the muscle cannot function properly. This may lead to collapse of the eye contents and the development of enophthalmos[10].

Superior Tarsal Muscle

Superior tarsal muscle (STM) is another muscle known as Müller's muscle, which was first described by Müller in 1858. STM consists of smooth muscle fibres and is located in the upper eyelid. It originates from the inferior portion of the levator palpebrae superioris muscle (LPSM) and extends alongside it. The muscle inserts into the superior edge of the tarsus via a 1 mm tendon[11] (Figure 2).

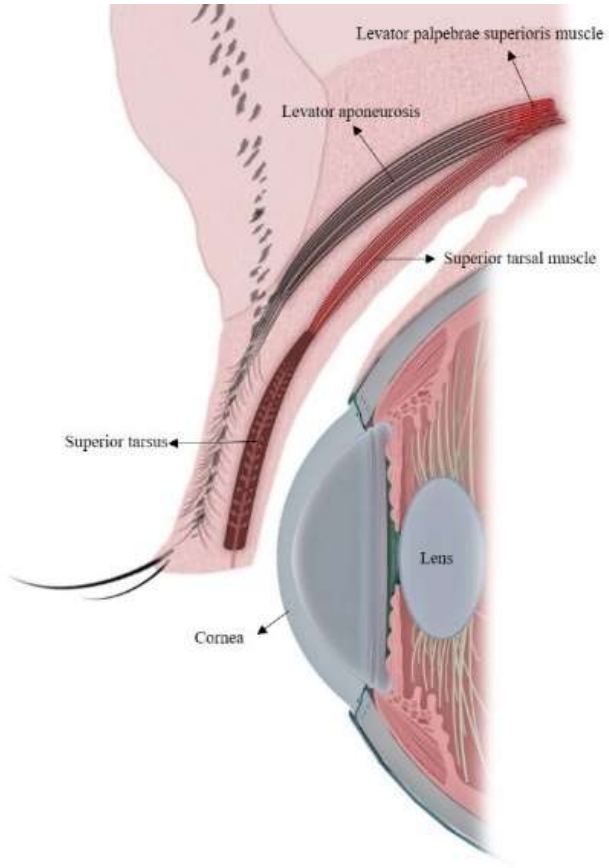


Figure 2. Schematization of the upper eyelid from the lateral view.

The LPSM aponeurosis is located in front of the muscle and the conjunctiva is located behind it. Superior tarsal muscle is approximately 15 mm wide, 10 mm long and 0.1-0.5 mm thick[12]. There is a transition area of loose connective tissue between the LPSM and STM fibres[13].

In some sources, smooth muscle fibres located deep in the LPSM are named as STM[7]. Thin smooth muscle fibres of the STM have differences that distinguish it from other smooth muscles. One of these differences is that STM contains not only smooth muscle fibres but also connective tissue and adipose tissue.

Furthermore, the smooth muscle cells of the muscle are sporadically spread out and not connected to each other[14].

Esperidião et al. classified the muscle into 4 patterns according to the attachment points to the superior tarsus.In Pattern 1, the muscle is observed to attach solely to the central portion of the upper tarsal margin. In Pattern 2M, the muscle is seen to attach to both the central and medial parts of the upper tarsal margin. In Pattern 2L, the muscle is observed to attach to both the central and lateral parts of the upper tarsal margin. In Pattern 3, the muscle is seen to attach to the entire extension of the upper tarsal border, spanning from the medial palpebral ligament to the lateral palpebral ligament. According to the results of the study, 63.27% of the cases were classified as P3, 24.49% as P2M, 8.16% as P2L and 4.08% as P1[13].

The upper eyelid is mainly raised by the LPSM. On the other hand, STM provides an extra 2 mm eyelid elevation in the upper eyelid in case of sympathetic system dominance[11,15]. Furthermore, it plays an active role in maintaining the tone of the elevated eyelid and ensuring the size of the palpebral fissure remains constant[16].

STM is arterial supplied by the lateral muscular branch of the ophthalmic artery. This branch also provides arterial supply to the lateral rectus, superior rectus, superior oblique and levator palpebrae superior muscles. The medial muscular branch of the ophthalmic artery supplies the other extraocular muscles. The venous blood drains into the vorticose veins and superior ophthalmic vein, and finally into the cavernous sinus[7,17].

The muscle is innervated by the sympathetic system. The postganglionic sympathetic fibres, which originate from the superior cervical ganglion, form a plexus around the internal carotid artery. The nerve fibres that leave the plexus enter the cranium and reach the cavernous sinus. The nerve fibres ultimately reach the orbit and then this muscle as a tightly wrapped nerve plexus encircling the ophthalmic artery, a branch of the internal carotid artery[7,17].

In the study reported by Yuzuriha et al., the STM was found to function as a mechanoreceptor via the stimulation of proprioceptive fibres. It also responds to the stimulation of sympathetic fibres[18]. Furthermore, Landau-Prat et al. have indicated that the Müller's muscle contains substantial myelinated sensory fibres that facilitate proprioceptive innervation[19].

Skeletal muscle fibres in the LPSM are intertwined with smooth muscle fibres in the STM. The opening of the upper eyelid with micro-movements or voluntary contractions of fast-twitch fibres in the LPSM stretch the mechanoreceptors in the STM. The resulting stimulus is conveyed to the mesencephalic trigeminal nucleus via the ophthalmic branch of the trigeminal nerve. Activation of the mesencephalic trigeminal nucleus results in the stimulation of the rostral locus coeruleus. The rostral locus coeruleus plays a role in regulating physiological arousal, which increases the microsaccade rate. Stretching of mechanoreceptors in the STM initiates reflex contractions of slow contractile fibres in the ipsilateral LPSM and frontalis muscle via the mesencephalic trigeminal nucleus[20]. It also initiates prolonged reflex contractions of slow-twitch fibres in the bilateral frontalis muscles and orbicularis oculi muscles for coordinated eye-eyelid-brow movements via the rostral locus coeruleus[21].

This muscle plays an active role in the opening of the eyelid and in clinical conditions in which it is affected, partial ptosis (drooping of the upper eyelid) is observed. Horner's syndrome, one of these clinical conditions, is usually caused by trauma to the neck and shoulder regions and consequent damage to the cervical sympathetic ganglia. As a consequence of this lesion, a ptosis of the upper eyelid of 2 to 3 mm is observed, resulting from paralysis of the STM, which has sympathetic innervation[11,22]. Conversely, exophthalmos (protrusion of the eyes forward) is observed in pathologies associated with hyperthyroidism, wherein the upper tarsal muscle displays hyperactivity[13].

Leshno et al. suggested the presence of eyelid-light reflex mediated by STM that occurs with sympathetic stimulation in the transition from light to dark conditions[23]. In their study, an average 8.3% retraction of the upper eyelid was observed with pupil dilation in the transition to the dark environment. Consequently, it has been reported that the STM expands the palpebral opening by adapting to the increase in pupil diameter to allow more light to enter the eye. This response may be referred to as the eyelid-light reflex[23].

In cases with a ptosis of less than 3 mm and a good function of the superior levator palpebrae muscle, a resection of the superior tarsal muscle is performed. Due to the high variability of the superior tarsal muscle, attention should be paid to its morphology in eyelid surgery[24].

Circular Fibers of the Ciliary Muscle

A section of the smooth muscle fibers located in the ciliary body of the eye also has the eponym Müller's muscle[25].

The ciliary body is a ring-shaped structure located in the vascular layer of the eye, between the iris and the choroidea. The width of the ring is approximately 5.9 mm on the nasal side and 6.7 mm on the temporal side[26]. In sagittal section, it has a triangular shape and the base of the triangle faces the anterior chamber. The apex of the triangle is located posteriorly in the ora serrata. While it is attached to the sclera externally, it occupies the posterior chamber and a small part of the vitreous cavity internally. The posterior part of the ciliary body, terminating at the ora serrata, is smooth, while its inner side contains numerous folds or projections extending into the posterior chamber. Lens zonules starting from the inner part connect the ciliary body to the lens (Figure 3). The ciliary body has two main functions: Aqueous humour production and accomodation[25].

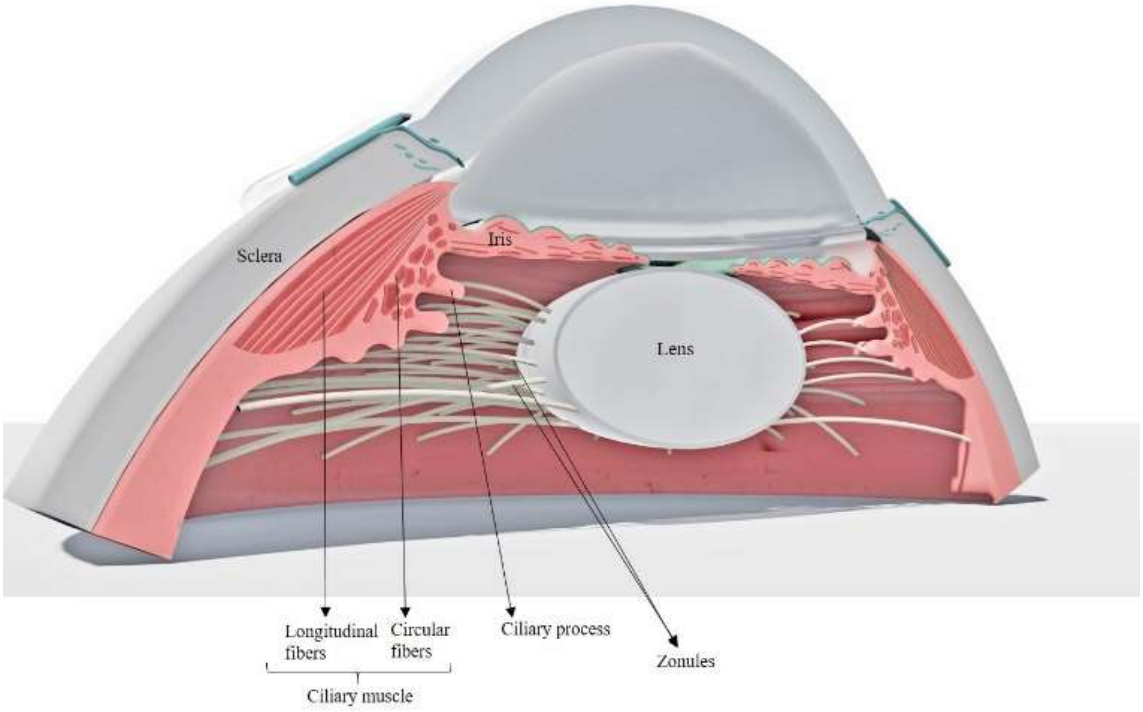


Figure 3. Visual modeling of eye cross-section

The ciliary body consists of the ciliary epithelium, ciliary body stroma, and ciliary muscle layer. The ciliary muscles consist of three bundles of smooth muscle fibers (longitudinal, radial, and circular) located in the anterior two-thirds of the ciliary body. They adjust the tension of the lens zonules to accommodate near and far vision. The fiber bundles embedded in the vascular connective tissue stroma are intertwined. These muscle fibers are named after scientists who described the anatomy of the ciliary body, such as Brücke, Müller and Ivanoff. Brücke described longitudinal muscle fibers; Ivanoff described radial/oblique muscle fibers; Müller described circular smooth muscle fibers[27].

The longitudinal fibers described by Brücke are the outermost layer of the ciliary muscle and run parallel to the sclera in the anterior third of the choroid. It starts from the scleral spur and adjacent corneoscleral trabeculae and attaches posteriorly to the anterior part of the choroid. The fibers are on average 3.4 mm

long[27]. The length of the Brücke's muscle increases with increasing axial length of the eye, whereas its cross-sectional area is independent of axial length[27,28].

The middle layer contains radial/oblique fibers, also called Ivanoff's muscle. This layer is the transition from longitudinal fibers to circular fibers[27].

The circular muscle fibers on the inside of the ciliary muscle are another muscle in the orbit called Müller's muscle. It is located in the connective tissue at the base of the ciliary processes. Circular fibers act as a sphincter for the ciliary body[26]. Both Müller's and Ivanoff's muscle fibers are fixed to the muscle elastic tissue to which the iris dilator muscle attaches[29].

Mao et al. measured the maximum thickness of Müller's and Iwanoff's muscles as 245 ± 125 μm and cross-sectional area as 0.19 ± 0.11 mm^2. The cross-sectional area of Müller's and Ivanoff's muscles decreases with increasing axial length[27].

The ciliary muscles are innervated by the autonomic nervous system. Parasympathetic stimulation provides contraction, while sympathetic stimulation produces an inhibitory effect. The cell bodies of the nerve fibers providing parasympathetic innervation are located in the parasympathetic nucleus (Edinger-Westphal) of the oculomotor nerve. Presynaptic fibers travel through the oculomotor nerve and synapse with postsynaptic cell bodies in the ciliary ganglion. Postsynaptic parasympathetic fibers reach the ciliary muscles via the short ciliary nerves. Contraction of Brücke's muscle pulls the choroid forward. Contraction of the Müller's muscle relaxes the lens zonules that lie between the ciliary processes and the lens. The tension of the lens decreases and the lens becomes thicker and more refractive. This allows the eye to focus on nearby objects (accommodation). In addition, contraction of the Brücke's muscle pulls the scleral spur backward, expanding the trabecular meshwork and thus facilitating drainage of the humor aquosus[25,26,30].

Presynaptic sympathetic neuron cell bodies are located in the lateral gray horn of the first thoracic segment of the spinal cord. After synapsing in the superior cervical ganglion, the postsynaptic fibers travel in the plexus around the internal carotid artery. These fibers join branches from the internal carotid plexus or the nasociliary nerve and reach the orbit. Fibers passing through the ciliary ganglion without synapsing reach the muscles. With sympathetic effect, ciliary muscle fibers relax and the eye goes into a resting state and is used for distance vision[25].

While the amount of connective tissue between the ciliary muscle fibers increases over time, the contractile strength of the ciliary muscle does not decrease over time[31].

Problems with the drainage of aqueous humor cause an increase in intraocular pressure and may result in glaucoma. In the presence of glaucoma, the cross-sectional area of the Müller's and Ivanoff's muscles decreases, while the dimensions of the Brücke's muscle are not affected by glaucoma[27].

Conclusion

The eponym "Müller's muscle" has been used in various textbooks, anatomy atlases, and articles across medical and health fields. In Snell's work, the term 'Müller's muscle' refers exclusively to the orbital muscle, while in Sobotta, it refers to the ciliary muscle. The atlases of Netter, Lippincott, and Prometheus use the term solely for the tarsalis superior muscle. Grays' Anatomy uses the term for both the orbital muscle and the tarsalis superior muscle. Additionally, some articles discussing "Müller's muscle" do not specify which muscle is being referred to.

This study provides topographic, clinical, and functional anatomical information about the orbital muscle, tarsalis superior muscle, and circular fibers of the ciliary muscle, all of which are referred to as "Müller's muscle" (Table 1). We believe that the fact that the term 'Müller's muscle' is used for different anatomical structures in the literature is an issue that requires attention from a terminological perspective. Consequently, we believe this study can help prevent confusion regarding the definition of these muscles, collectively known as "Müller's muscle."

Table 1. Comparison of Superior Tarsal Muscle, Orbital Muscle and Circular Fibers of the Ciliary Muscle

	Orbital Muscle	Superior Tarsal Muscle	Circular Fibers of the Ciliary Muscle
Location	Located in the lower part of the orbit, in the infraorbital fissure.	Located on the deep surface of the levator palpebrae superioris muscle in the upper eyelid.	Located in the anterior two-thirds of the ciliare body
Function	Maintains orbital content position and provides structural tone.	Assists in elevating the upper eyelid by a few millimeters.	Provides near vision (accommodation) by changing the tension of the ciliary zonule.
Clinical significance	Enophthalmos may occur due to loss of sympathetic innervation.	Partial ptosis occurs in case of sympathetic denervation (Horner's syndrome).	Accommodation disorders and age-related conditions such as presbyopia

Acknowledgments: The authors would like to thank architect Yiğit Kağan KARAGÖZ for creating the illustrations.

References

1. Cornelius CP, Mayer P, Ehrenfeld M, Metzger MC. The Orbits— Anatomical features in view of innovative surgical methods. Facial Plast Surg. 2014;30:487–508.
2. Cho KH, Lee HS, Katori Y, Rodríguez-Vázquez JF, Murakami G, Abe S. Deep fat of the face revisited. Clin. Anat. 2013;26:347–56.
3. Wilden A, Feiser J, Wöhler A, Isik Z, Bendella H, Angelov DN. Anatomy of the human orbital muscle (OM): Features of its detailed topography, syntopy and morphology. Ann Anat. 2017;211:39-45.
4. De Battista JC, Zimmer LA, Theodosopoulos PV, Froelich SC, Keller JT. Anatomy of the inferior orbital fissure: implications for endoscopic cranial base surgery. J. Neurol. Surg. B: Skull Base. 2012;73:132–38.
5. Rodríguez-Vázquez JF, Mérida-Velasco JR, Arráez-Aybar LA, Jiménez-Collado J. Anatomic relationships of the orbital muscle of Müller in human fetuses. Surgical and Radiologic Anatomy. 1999;20:341-44.
6. Von Lanz T, Wachsmuth W. Praktische Anatomie. Kopf. Springer-Verlag, Berlin, 1979:481–82.
7. Standring S. Gray's Anatomy. 41st ed. Edinburgh: Elsevier Churchill Livingstone, 2016.
8. De Haan AB, Willekens B, Klooster J, Los AA, van Zwietwn J, Botha CP et al.. The prenatal development of the humanorbit. Strabismus. 2006;14:51–6.
9. Osanai H, Abe SI, Rodríguez-Vázquez J, Verdugo-López S, Murakami G, Ohguro H. Human orbital muscle: a new point of view from the fetal development of extraocular connective tissues. Investigative Ophthalmology & Visual Science. 2011;52:1501-06.
10. Arifoğlu Y. Her Yönüyle Anatomi. 3. Baskı. İstanbul, İstanbul Tıp Kitabevi, 2021.
11. Finsterer J. Ptosis: Causes, Presentation, and Management . Aesth. Plast. Surg. 2003;27:193–204.
12. Beard C. Müller's superior tarsal muscle: anatomy, physiology, and clinical significance. Ann Plast Surg. 1985;14:324-33.
13. Esperidião-Antonio V, Conceição-Silva F, De-Ary-Pires B, Pires-Neto MA, de Ary-Pires R. The human superior tarsal muscle (Müller's muscle): a morphological classification with surgical correlations. Anat Sci Int. 2010;85:1-7.
14. Bang YH, Park SH, Kim JH, Cho JH, Lee CJ, Roh TS. The role of Müller's muscle reconsidered. Plast Reconstr Surg. 1998;101:1200-4.
15. Stewart JM, Carter SR. Anatomy and examination of the eyelids. Int Ophthalmol Clin. 2002;42:1.
16. Baldwin HC, Bhagey J, Khooshabeh R. Open sky Muller muscle-conjunctival resection in phenylephrine test-negative blepharoptosis patients. Ophthal Plast Reconstr Surg. 2005;21:276–80.
17. Moore KL, Dalley AF, Agur AMR. Clinically Oriented Anatomy.7th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2014.
18. Yuzuriha S, Matsuo K, Hirasawa C, Moriizumi T: Refined distribution of myelinated trigeminal proprioceptive nerve fibres in Mueller's muscle as the mechanoreceptors to induce involuntary reflexive contraction of the levator and frontalis muscles. J Plast Reconstr Aesthet Surg. 2009;62:1403-10.
19. Landau-Prat D, Mayer C, Gomel N, Arazi M, Zloto O, Dori A, & Simon GJB. Müller's Muscle as a Sensory Proprioceptive Organ: Histological and Histochemical Analysis. Investigative Ophthalmology & Visual Science. 2023;64:18-18.
20. Ban R, Matsuo K, Osada Y, Ban M, & Yuzuriha S. Reflexive contraction of the levator palpebrae superioris muscle to involuntarily sustain the effective eyelid retraction through the transverse trigeminal proprioceptive nerve on the proximal Mueller's muscle: verification with evoked electromyography. Journal of plastic, reconstructive & aesthetic surgery. 2010;63:59-64.
21. Matsuo K, & Kaneko A. Stretching of Mechanoreceptors in Superior Tarsal Muscle Reflexively Contracts Slow-Twitch Fibers in Facial Expression Muscles: A Case Series. Cureus. 2024;16:e64438.

22. Murchison AP, Bilyk JR, Savino PJ. Ptosis in neurologic disease. Smith and Nesi's Ophthalmic Plastic and Reconstructive Surgery. 2021;243-78.
23. Leshno A, Smadar L, Kapelushnik N, Serlin T, Prat D, Priel A, & Sagiv O. New insight into the physiologic function of Müller's muscle. Experimental Eye Research. 2021;202:108336.
24. Ben Simon GJ, Lee S, Schwarcz RM et al. Muller's muscle-conjunctival resection for correction of upper eyelid ptosis: relationship between phenylephrine testing and the amount of tissue resected with final eyelid position. Arch Facial Plast Surg. 2007;9:413-17.
25. Forrester JV, Dick AD, McMenamin PG, Roberts F, Pearlman E. The Eye: Basic Sciences in Practice. 5th ed. UK, Saunders/Elsevier. 2021.
26. Remington LA, & Goodwin D. Clinical Anatomy and Physiology of the Visual System. 4th ed. Elsevier Health Sciences. 2022.
27. Mao Y, Bai HX, Li B, Xu XL, Gao F, Zhang ZB, Jonas J. B. Dimensions of the ciliary muscles of Brücke, Müller and Iwanoff and their associations with axial length and glaucoma. Graefe's Archive for Clinical and Experimental Ophthalmology. 2018;256: 2165-71.
28. Park CY, Lee JK, Kahook MY, Schultz JS, Zhang C, Chuck RS. Revisiting ciliary muscle tendons and their connections with the trabecular meshwork by two photon excitation microscopic imaging. Invest Ophthalmol Vis Sci. 2016;57:1096–1105.
29. Flügel-Koch CM, Tektas OY, Kaufman PL, et al. Morphological alterations within the peripheral fixation of the iris dilator muscle in eyes with pigmentary glaucoma. Invest Ophthalmol Vis Sci. 2014;55:4541–51
30. Warjri GB, & Senthil S. Imaging of the Ciliary Body: A Major Review. Seminars in Ophthalmology, 2022;37:711–23.
31. Strenk SA, Strenk LM, Guo S. Magnetic resonance imaging of aging, accommodating, phakic, and pseudophakic ciliary muscle diameters. J Cataract Refract Surg. 2006;32:1792–1798.

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Risky Baby Rehabilitation

Riskli Bebek Rehabilitasyonu

Tuba Tülay Koca[1]

[1]Sütçü İmam University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Kahramanmaraş, Türkiye

ABSTRACT

When we look at the definition of risky babies, the first to come to mind is preterm babies born before the 32nd week of pregnancy, but also postterm newborns, term low birth weight babies (<2500 gr), and babies with congenital anomalies are included in this class. With developing technology, it is possible to keep more risky babies alive. It is known that premature babies, compared to term babies, show suboptimal motor development behavior and self-regulation problems in all subsystems (mental, developmental, neurobehavioral, motor) in the 3rd and 6th months of their follow-up.

Early neurodevelopmental assessments of high-risk newborns should be performed, deficiencies should be determined, and physiotherapeutic intervention and family-centered rehabilitation programs should be initiated early in the needed areas. Although premature babies are thought to have problems only in the motor area, they now have difficulties in many neurodevelopmental stages, such as social, behavioral, life skills, sleep, language, nutrition, mental health, toilet habits, and communication. Some premature babies are diagnosed with autism and attention deficit, and hyperactivity disorder over time. This group of children with special needs should be closely monitored at every stage of their lives.

10% of preterm babies are diagnosed with cerebral palsy later in life. Cerebral palsy presents with non-progressive damage to the central nervous system as well as progressive problems in the musculoskeletal system. Parents, who were left out of treatment processes in the past, are now at the center of the rehabilitation team. It should be kept in mind that healthy babies will become healthy adults in the future.

Keywords: risky baby, rehabilitation, neurodevelopmental assessment, prematurity, cerebral palsy

ÖZET

Riskli bebek tanımına baktığımızda ilk olarak 32. gebelik haftasında önce dünyaya gelen preterm bebekler gelmekle birlikte postterm yenidoğanlar, term doğan düşük doğum ağırlıklı bebekler (<2500 gr), konjenital anomalili bebekler de bu sınıfta yer almaktadır. Gelişen teknolojiyle birlikte daha çok riskli bebekleri hayatta tutunabilmektedir. Prematüre bebeklerin, term bebeklere göre takiplerinin 3. ve 6. aylarında optimal olmayan motor gelişim davranışı ve tüm alt sistemlerde (zihinsel, gelişimsel, nörodavranışsal, motor) özdüzenleme sorunları gösterdiği bilinmektedir.

Yüksek riskli yenidoğanların nörogelişimsel değerlendirmelerinin erken yapılması, eksikliklerinin belirlenmesi ve ihtiyaç duyulan bölgede fizyoterapötik müdahale ve aile merkezli rehabilitasyon programlarının erken başlatılması gerekmektedir. Prematüre bebekler sadece motor alanda sorun yaşadığı düşünülse de artık sosyal, davranış, yaşam becerileri, uyku, dil, beslenme, ruh sağlığı, tuvalet alışkanlıkları ve iletişim gibi pek çok nörogelişimsel aşamada zorluk yaşamaktadır. Erken doğan bazı bebeklere zamanla otizm ve dikkat eksikliği ve hiperaktivite bozukluğu tanısı konur. Bu özel ihtiyaçları olan çocuk grupları hayatlarının her döneminde yakından takip edilmelidir.

Preterm bebeklerin %10'u hayatlarının ilerleyen dönemlerinde serebral palsi tanısı almaktadır. Serebral palsi santral sinir sistemindeki non-progresif hasarın yanında musküloskeletal sistemde progresif problemler ile karşımıza çıkmaktadır. Geçmiş yıllarda tedavi süreçlerinde dışarıda bırakılan ebeveynler artık rehabilitasyon ekibinin merkezinde yer almaktadırlar. Sağlıklı bebeklerin gelecekte sağlıklı yetişkinler olacağı akılda tutulmalıdır.

Anahtar kelimeler: Riskli bebek, rehabilitasyon, nörogelişimsel değerlendirme, prematürite, serebral palsi

Correspondence Address / Yazışma Adresi
Tuba Tülay Koca, Sütçü İmam University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Kahramanmaraş, Türkiye
e-mail: tuba_baglan@yahoo.com

2025;34(3):237-242
doi:10.17827/aktd.1566677
Geliş tarihi/ Received: 14.10.2025
Kabul tarihi/Accepted: 16.07.2025

Introduction

With the developing technologies in the field of health, we can now keep more risky babies alive. Teratogenicity is also increasing due to reasons such as increasing environmental pollution, ionizing radiation, infections, and exposure to chemical and toxic substances in air, water, or nutrition. For this reason, health services now encounter a higher number of risky babies, and these babies cause high health expenses due to their needs. Prematurity seems to be particularly related to the mother's socioeconomic level and lifestyle, and its incidence is reported to be approximately 11% of all live births. While the preterm birth rate in Türkiye is reported as 12.9% in 2022, this rate is reported as 10-11% in the world after 2020. This rate may vary depending on the development level of the countries1,2. Preterm birth continues to pose a serious burden on healthcare systems around the world. In this review, high-risk newborns will be defined, and neurodevelopmental evaluation and early physiotherapeutic intervention programs will be summarized in light of current literature.

Definition of a Risky Baby

When we look at the definition of risky baby, babies born before the 37th gestational week come first, but babies weighing less than 2500 g (low birth weight), post-term babies, large babies, babies born with congenital cardiac, central nervous system or orthopedic defects are also included in the risky baby category.

High Risk Newborn;

I. Low birth weight:

* Term and low birth weight (<2500 g), LBW
* Very low birth weight (<1500 g), VLBW
* Very very low birth weight (<1000 g), VVLBW

II. Low weight for gestational age (SGA = small gestational age)

III. Large for gestational age (LGA): large baby

IV. Postterm

V. Premature and preterm baby

In premature newborns, hemodynamic and vital problems are first addressed in the intensive care unit. Corticosteroid administration for lung maturation, Vitamin K, especially for intracranial bleeding prevention, protection against eye infections and other systemic infections, and thermoregulation problems (Kangaroo mother care, protective wrapping, and dyspnea can be given as examples.

Neurorehabilitation begins in intensive care; It includes multisensory positive experiences that include vocals, smell, and touch, and motor training that includes massage and physical therapy. Especially preterm newborns need to be evaluated in terms of congenital anomalies such as the central nervous system, musculoskeletal system, and cardiopulmonary system.

Babies born before the 32nd week of gestation, have a significantly increased risk of audiovisual, cognitive, social, and motor disorders. Some term babies may develop hypoxic-ischemic encephalopathy due to hypoxia in the neonatal period. Cerebral palsy may also develop in up to 10% of premature babies. Many more babies are diagnosed with milder disorders later in life, including autistic spectrum disorder, mild cognitive and motor impairment, and attention-deficit/hyperactivity disorder. Today, we know that neurodevelopmental problems occur in the long term (adolescent and adult) in prematurity [3].

Risky Baby Rehabilitation

It aims to support the development of babies, improve their physical and cognitive skills, ensure their nutrition, and prevent possible complications. Risky baby rehabilitation is an important process for babies and often requires a transdisciplinary approach and is customized according to the baby's needs. While

physiotherapy focuses on improving babies' muscle tone and motor skills, speech therapy supports babies' communication skills, and nutritionists create a nutrition plan tailored to babies' needs.

Premature babies may experience weakness in body muscles in the early period, delay in movements such as turning, sitting, crawling, and walking, lack of sucking and swallowing skills, and delay in speech in the later period. High-risk babies may have difficulty calming themselves down, cry frequently, and avoid movement. They may experience sensory issues such as hyperactivity or needing too much stimulation. The prevalence of these problems increases with lower gestational age and birth weight. Additionally, learning disabilities, clumsiness, developmental coordination problems, social-emotional difficulties, and other minor dysfunctions are also reported. Even at term age, the central nervous system is not mature enough to show pathological findings associated with corticospinal lesions. Therefore, because the motor pathways of preterm babies have not yet matured, the emergence of early atypical neuromotor patterns may not be associated with neurodevelopmental outcomes at later ages. Clinicians aim to ensure early diagnosis of developmental disorders and identification of preventive programs through neurodevelopmental assessments (NFA)[1-4].

Neurodevelopmental Assessments (NFA)

What steps should be taken to improve outcomes in premature babies? NFA focuses on the development of normal functions and is based on studies on stimulated and spontaneous motility, postural adaptation, variability in motor patterns, neurosensory function, and neuromotor and behavioral skills[5].

The neurocognitive outcomes of preterm babies are poorer than those of term babies for many reasons, including brain damage and altered brain development. However, poor outcomes appear to be more closely related to the mother's socioeconomic status than to problems the baby may experience after birth. Additionally, prematurity is increasing in developing societies. Early intervention programs start in the first 24 months and continue until the school year. The main goal of these programs is to make the child as functionally independent as possible by using brain plasticity. Intervention programs conducted by many different centers are conceptually attractive but have not been consistently successful, and we do not have sufficient data on long-term outcomes[6].

Diagnosis of Cerebral Palsy in Early Period

The definition of cerebral palsy is characterized by progressive problems in the musculoskeletal system due to non-progressive damage to the central nervous system due to prenatal, natal, or postnatal reasons, as well as problems in cognition, perception, behavior, social, and communication. Early detection is important for the success of the rehabilitation process. So, it is important to diagnose a child with cerebral palsy in early period.

Prechtl's general movements (GMs) assessment can be used by clinicians as a diagnostic tool to recognize cerebral palsy in the early months. In healthy newborns, GMs can be observed until the end of the first 6 months and are based on the presence of complexity, homogeneity, and rhythmicity in all body extremity movements. In children with cerebral palsy, this movement is more monotonous and weak. Loss of fidgety movements is a guide for the prognosis of the newborn baby[7].

Neurodevelopmental Assessment Scales

These scales play a role in recognizing organic central nervous system problems in the early period and determining the deficiency in which neurodevelopmental steps are present, and thus provide guidance in determining the rehabilitation of at-risk babies and children.

Wechsler Scales, Behavior Assessment System for Children (BASC), Wechsler Memory Scale, Minnesota Multiphasic Personality Inventory (MMPI), Beck Depression Inventory (BDI), Boston Naming Test, Halstead-Reitan Neuropsychological Battery (HRNB), Tactual Performance Test and Sensory Perceptual Examination), Hand Grip Strength, Alberta Baby Motor Scale (AIMS), Peabody Developmental Motor Scale, Bayley Developmental Scale, Gesell Developmental test, Denver Developmental Screening test are some of them. These scales help plan early intervention and rehabilitation programs by evaluating babies'

motor, language, social, and personality skills. These scales have strengths and weaknesses towards each other[8].

Family-Centered Physiotherapeutic Rehabilitation in the Early Period

Many factors can affect fetal growth and development, so these children should be included in early rehabilitation programs to stimulate brain plasticity. An educated parent plays a key role in the rehabilitation team [9].

Various early physiotherapeutic intervention programs should be developed for preterm children with motor impairment. Unfortunately, no evidence is available on whether physiotherapeutic intervention programs for babies have a positive effect on long-term motor outcomes. Until about twenty years ago, traditional physiotherapeutic approaches focused only on the child's motor development. Since then, problems in cognitive, sensory, and social skill components, as well as motor development, have been recognized and a dynamic treatment process has been focused on that makes families the center of treatment.

Family-centered care, which recognizes the importance of involving family members as active and equal partners in the child's care, has become the preferred practice. The treatment goals of these centers are; to bring the relationship between mother-baby, and baby-environment to the most optimal level and to create a dynamic, developing treatment process. Parents should aim to support the baby's subsystem functioning, self-regulation strategies, competencies, attention and development, brain organization, development, increasing learning opportunities, improving communicative perceptions, and facilitating the desire to participate in the outside world. Current family-centered communication-focused intervention programs should be continued[10].

Bobath neurodevelopmental therapy is a widely used method around the world to support the baby's sensory and motor development especially in hemiplegic cerebral palsy. Its goal is to ensure the child's functional independence and it includes sub-techniques such as environmental adaptations, providing parental communication, facilitation techniques, and assessment of tasks[11].

Coping with and Caring for Babies with Special Needs (COPCA), developed approximately 15 years ago. It is a family-centered early physiotherapeutic intervention program. It includes a family and education component and a neurodevelopmental component. It has been observed that premature children born before 32 weeks without significant organic central nervous system damage showed better motor recovery with the family-centered COPCA program than with standard physiotherapy programs[12].

It is known that preterm babies show non-optimal motor development behavior and self-regulation problems in all subsystems (mental, developmental, neurobehavioral, motor) at the 3rd and 6th months of follow-up compared to term babies[13]. Preterm babies are at high risk for motor developmental delays, learning difficulties, and behavioral problems. For these reasons, neurodevelopmental evaluation is essential. The risk of neurodevelopmental delay is especially high in children who develop sepsis and necrotizing enterocolitis (NEC)[14].

Neonatal behavioral characteristics such as hypersensitivity and poor state regulation are associated with high levels of crying. Frequent crying behavior, especially in premature babies, indicates that these babies are hypersensitive, need high sensory input, and have poor adaptation abilities in disturbing situations. Clinical evaluations based on the newborn behavior assessment scale may help parents to clarify their babies' tolerance level to stimuli and to develop awareness of this issue[15]. Studies Show that early combined rehabilitation interventions (auditory, visual stimulation, oral motor function, respiratory functions, and neurodevelopmental training) improve short-term clinical outcomes in premature babies[16].

In the study of Danks M et al. which investigated whether behavioral problems were related to motor abilities in pre-adolescent children with a history of very low birth weight, no relationship was observed, but it was observed that supporting motor competence in 11-13-year-old preteen children with low birth weight provided improvements in social behavior and attention. As a result, mild motor impairment was associated with poor attention and low social behavior, independent of low birth weight[17].

Drawing is a graphomotor skill used early in assessing visual-motor coordination. In a retrospective study of 50 children aged 12-36 months to determine the frequency of graphomotor difficulties in children with perinatal central nervous system disorders and premature birth, only 13 children had graphical abilities below those expected for their age. One child couldn't used a pencil. The remaining 72% was found normal. As a result, it was concluded that there is a risk of developing difficulties in learning, attention, and fine motor skills in preterm children during the preschool period[18].

High-risk babies may experience neurodevelopmental delays and problems in many areas later in life. These babies reflect these disorders into adolescence, youth, and adulthood (autism, attention deficit hyperactivity disorder, and other neurodevelopmental disorders). Healthcare expenses for risky babies are also high. This group with special needs should be closely monitored at every stage of their lives.

Conclusion

All children born under the 32nd week of gestation should have neurodevelopmental evaluations in terms of developmental outcomes and need for therapeutic support; their needs should be determined, and they should be included in family-centered physiotherapeutic intervention programs in the early period in cooperation with parents. Not every child may have needs in all areas. Infants at risk may have needs in different areas such as behavior, communication, language, sensory, nutrition, toilet habits, mental health, life skills, sleep, learning, and developmental needs. Parents should be equipped to determine their children's needs through neurodevelopmental evaluations, and the rehabilitation process should begin.

References

1. Ohuma EO, Moller AB, Bradley E, Chakwera S, Hussain-Alkhateeb L, Lewin A et al. National, regional, and global estimates of preterm birth in 2020, with trends from 2010: a systematic analysis. Lancet. 2023;402:1261-1271. doi: 10.1016/S0140-6736(23)00878-4. Erratum in: Lancet. 2024;403(10427):618. doi: 10.1016/S0140-673600267-8.
2. Harrison MS, Goldenberg RL. Global burden of prematurity. Semin Fetal Neonatal Med. 2016;21:74-9. doi: 10.1016/j.siny.2015.12.007.
3. Cheong JLY, Burnett AC, Treyvaud K, Spittle AJ. Early environment and long-term outcomes of preterm babies. J Neural Transm (Vienna). 2020;127:1-8. doi: 10.1007/s00702-019-02121-w.
4. Koldewijn K, van Wassenaer A, Wolf MJ, Meijssen D, Houtzager B, Beelen A et al. A neurobehavioral intervention and assessment program in very low birth weight babies: outcome at 24 months. J Pediatr. 2010;156:359-65. doi: 10.1016/j.jpeds.2009.09.009.
5. Picciolini O, Montirosso R, Porro M, Giannì ML, Mosca F. Neurofunctional assessment at term equivalent age can predict 3-year neurodevelopmental outcomes in very low birth weight babies. Acta Paediatr. 2016;105:e47-53. doi: 10.1111/apa.13248.
6. Koldewijn K, van Wassenaer A, Wolf MJ, Meijssen D, Houtzager B, Beelen A et al. A neurobehavioral intervention and assessment program in very low birth weight babies: outcome at 24 months. J Pediatr. 2010;156:359-65. doi: 10.1016/j.jpeds.2009.09.009.
7. Einspieler C, Prechtl HF. Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system. Ment Retard Dev Disabil Res Rev. 2005;11:61-7. doi: 10.1002/mrdd.20051.
8. Hadders-Algra M, Tacke U, Pietz J, Rupp A, Philippi H. Standardized Baby NeuroDevelopmental Assessment developmental and socio-emotional scales: reliability and predictive value in an at-risk population. Dev Med Child Neurol. 2020;62:845-53. doi: 10.1111/dmcn.14423.
9. Mikelić VM, Bartolović J, Kosicek T, Crnković M. Educated parent as a key member of rehabilitation team. Acta Clin Croat. 2011;50(4):469-73.
10. https://ibaip.org/
11. Tekin F, Kavlak E, Cavlak U, Altug F. Effectiveness of Neuro-Developmental Treatment (Bobath Concept) on postural control and balance in Cerebral Palsied children. J Back Musculoskelet Rehabil. 2018;31:397-403. doi: 10.3233/BMR-170813.
12. Akhbari ZS, von RM, Meichtry A, Wirz M, Hielkema T, Hadders-Algra M. Swiss Neonatal Network & Follow-Up Group. The Coping with and Caring for Babies with Special Needs intervention was associated with improved motor development in preterm babies. Acta Paediatr. 2021;110:1189-1200. doi: 10.1111/apa.15619.
13. Koldewijn K, Wolf MJ, van Wassenaer A, Meijssen D, van Sonderen L, van Baar A et al. The Baby Behavioral Assessment and Intervention Program for very low birth weight babies at 6 months corrected age. J Pediatr. 2009;154:33-38.e2. doi: 10.1016/j.jpeds.2008.07.039.
14. Picciolini O, Montirosso R, Porro M, Giannì ML, Mosca F. Neurofunctional assessment at term equivalent age can predict 3-year neurodevelopmental outcomes in very low birth weight babies. Acta Paediatr. 2016;105:e47-53. doi: 10.1111/apa.13248.
15. Ohgi S, Gima H, Akiyama T. Neonatal behavioural profile and crying in premature babies at term age. Acta Paediatr. 2006;95:1375-80. doi: 10.1080/08035250600602984.
16. Liu Y, Li ZF, Zhong YH, Zhao ZH, Deng WX, Chen LL et al. Early combined rehabilitation intervention to improve the short-term prognosis of premature babies. BMC Pediatr. 2021;21:269. doi: 10.1186/s12887-021-02727-8.

17. Danks M, Cherry K, Burns YR, Gray PH. Are behaviour problems in extremely low-birthweight children related to their motor ability? Acta Paediatr. 2017;106:568-572. doi: 10.1111/apa.13712.
18. Matijević-Mikelić V, Kosicek T, Crnković M, Trifunović-Macek Z, Grazio S. Development of early graphomotor skills in children with neurodevelopmental risks. Acta Clin Croat. 2011;50:317-21.

Arşiv Kaynak Tarama Dergisi
Archives Medical Review Journal

DERLEME/REVIEW

Alternative Medicine for Gonarthrosis Pain

Gonartroz Ağrısında Alternatif Tıp Tedavileri

Ahmet Issın[1]

[1]Çanakkale Onsekiz Mart University Faculty of Medicine. Department of Orthopaedics and Traumatology, Çanakkale, Türkiye

ABSTRACT

Osteoarthritis is the most common joint disorder characterized by the gradual deterioration of articular cartilage, in osteoarthritis, not only the joint cartilage, but also all surrounding tissues, including the synovium, subchondral bone, joint capsule, ligaments, periarticular muscles, and nerves are affected and contribute to the pain. The knee is the most common location for this disease, known as gonarthrosis. In the late stages of the disease surgery is the definitive treatment; however before that stage patients seek pain relieving methods for years resulting in repeated visits to physicians. Eventually, they may run out of treatment options and feel desperate.

This review investigates the methods of alternative-medicine for alleviating pain in gonarthrosis patients. Alternative treatments, including prolotherapy with intra-tissue substance injection, radiotherapy, and ozone therapy for modifying chemical balances, are explored for their plausibility and safe side effect profiles. However, the review discourages wet-cupping and leech therapy due to potential infection risks. Ancient practices like acupuncture and reflexology, lacking scientific backing for their mechanisms of action, are criticized. Homeopathy is categorically dismissed as quackery, and caution is advised against cure-all drugs with extravagant promises.

Navigating the intricate interplay of facts and lies, the article underscores the ethical responsibility of physicians, emphasizing the application of scientific truths and the art of medicine which also consist of addressing the patients concerns, reassuring and satisfying them. The review concludes that alternative-medicine should be considered within the medical realm solely for those specific soothing purposes, urging a cautious and evidence-based approach.

Keywords: gonarthrosis, prolotherapy, mesotherapy, hijamat, homeopathy, apitherapy, hirudotherapy, acupuncture, reflexology, cupping, phytotherapy, aromatherapy, herbalism, radiotherapy, ozone

ÖZET

Osteoartrit, eklem kıkırdağının peyderpey bozulmasıyla karakterize en yaygın bir eklem hastalığıdır; osteoartritte yalnızca eklem kıkırdağı değil aynı zamanda sinoviyum, subkondral kemik, eklem kapsülü, bağlar, periartiküler kaslar ve sinirler de dahil olmak üzere eklem çevresindeki tüm dokular da etkilenir ve ağrıya katkıda bulunur. Dizde görüldüğünde gonartroz olarak adlandırılır. Hastalığın ileri evrelerinde nihai tedavi cerrahidir ancak bu evreden önce hastalar tekrar tekrar hekimlere başvurur ve yıllarca çeşitli ağrı giderici yöntemleri denerler. Sonuç olarak tıbbi tedavi seçenekleri tükenebilir ve bazen çaresizce alternatif yöntemlere başvururlar.

Bu derlemede gonartroz hastalarında ağrının azaltılmasına yönelik alternatif tıp yöntemleri gözden geçirilmiştir. Doku içi madde enjeksiyonu ile proloterapi, kimyasal dengeleri değiştirme potansiyeli olan radyoterapi ve ozon uygulamaları etki mekanizmalarının mantık dahilinde olması ve güvenli yan etki profilleri açısından makul bulunmuştur. Ancak, potansiyel enfeksiyon riskleri nedeniyle ıslak hacamat ve sülük tedavisi uygun görülmemiştir. Akupunktur ve refleksoloji gibi etki mekanizmaları mantıktan uzak ve bilimsel olarak desteklenemeyen kadim uygulamalar eleştirilmiştir. Homeopati bir nevi şarlatanlık olarak ele alınmış, abartılı vaatlerle her şeyi tedavi ettiğini iddia eden ilaçlara karşı dikkatli olunması tavsiye edilmiştir.

Gerçekler ve yalanların iç içe girmesini eleştiren makale, hekimlerin etik sorumluluğunun bilimsel gerçeklere göre hareket etmenin yanısıra, hastaların endişelerini gidermeyi, onları rahatlatmayı ve tatmin etmeyi de içerdiğine vurgu yapmaktadır. Derleme, alternatif tıbbın yalnızca bu gibi teskin edici bazı amaçlar için değerlendirilmesi gerektiği sonucuna varmakta aslen ihtiyatlı ve kanıta dayalı yaklaşımları önermektedir.

Anahtar kelimeler: gonartroz, proloterapi, mezoterapi, hacamat, kupa, homeopati, apiterapi, hirudoterapi, sülük, akupunktur, refleksoloji, fitoterapi, aromaterapi, herbalizm, radyoterapi, ozon.

Correspondence Address / Yazışma Adresi
Ahmet Issın, Çanakkale Onsekiz Mart University Faculty of Medicine, Department of Orthopaedics and Traumatology, Çanakkale, Türkiye
e-mail: ahmet.issin@gmail.com

2025;34(3):243-252
doi:10.17827/aktd.1548783
Geliş tarihi/ Received: 20.09.2024
Kabul tarihi/Accepted: 24.07.2025

Introduction

Knee osteoarthritis (gonarthrosis) is a chronic, progressive condition prevalent in the general population that significantly impairs quality of life due to pain and restricted mobility. In advanced stages, surgical intervention is often the definitive treatment. However, in an effort to manage symptoms such as pain and joint stiffness, patients frequently turn to alternative medicine practices. This patient behavior places physicians in a position where they are routinely asked to comment on, or even recommend, such therapies. Accordingly, physicians need reliable, evidence-based information on these modalities.

This review aims to provide clinicians with an up-to-date synthesis of the available evidence primarily drawn from systematic reviews regarding the efficacy of selected alternative medicine approaches in managing knee osteoarthritis symptoms. The alternative methods discussed were specifically chosen because they are widely used in Türkiye and are formally included under the *Traditional and Complementary Medicine Practices Regulation,* which was established by the Ministry of Health in 2011. This regulation authorizes only licensed physicians and healthcare professionals under physician supervision to perform such practices.

The definition of alternative medicine has evolved into different names such as complementary medicine, integrative medicine, and holistic medicine primarily in response to criticism of the term "alternative". In fact, all these definitions point to the same pseudo-science phenomenon; they are no different from each other[1]. In certain countries, traditional medicine holds a significant cultural value and retains importance within societal practices. These nations often endorse ancient medical traditions as an integral component of health tourism. However, these endorsements are primarily driven by political considerations rather than scientific ones, given the substantial economic market, which exceeds hundreds of billions of dollars[2].

In the Turkish context, although the regulation attempts to impose clinical oversight, ethical guidelines remain paramount. Article 20 of the medical deontology regulation advises the physician not to give the patient a medicine that he knows is useless and not to incur unnecessary expenses. However, in cases where a real treatment is not possible, it is suggested that certain medications may be recommended for consolation, with a caveat that expensive palliative drugs should not be recommended to patients who cannot afford them[3]. It is the physician's foremost ethical responsibility to uphold these principles when recommending such treatment modalities.

Pain is the primary complaint in gonarthrosis, and pain reduction is the main goal of most alternative therapies. Given the well-established analgesic effect of the placebo response, recommending harmless alternative interventions may be ethically permissible. However, it is essential that such interventions are not misrepresented as curative, and patients should be advised to adhere to evidence-based medical care whenever possible.

There is a growing body of literature on alternative medicine approaches, but the quality and consistency of evidence vary widely. This review contributes to the field by offering a focused synthesis of methods that are both officially regulated in Türkiye and commonly used in practice. We conducted a thorough review of the current literature, focusing primarily on systematic reviews where available. Our aim was to provide concise insights into these methods that are gaining popularity, despite the ongoing uncertainty surrounding their effects.

Radiotherapy

Especially in Germany and Central European countries, low-dose radiotherapy has been used for a long time in painful diseases of the musculoskeletal system including gonarthrosis. In Germany over one-third of all radiotherapy treatments are for benign diseases, including over 15,000 patients with osteoarthritis however in the USA the use of radiotherapy for such an indication is almost nonexistent[4]. Although its mechanism of action is not fully known, but it is believed to act through multiple mechanisms: it is effective on mononuclear and polynuclear leukocytes, endothelial cells, and macrophages, in addition, it reduces the release of cytokines and proteolytic enzymes by increasing the permeability of the vascular endothelium, killing inflammatory cells such as lymphocytes, modulates the autonomic nervous system, and alters tissue pH. Side effects are negligible[5-7]. Typically, a dose of 0.5 to 1Gy is repeated 3 to 6 times at 2–3-week intervals.

Its analgesic effect is not acute, it appears in the late period, and some studies say that this effect lasts up to two years, so it is ideal in chronic painful conditions such as gonarthrosis[6-9]. Although there were some studies in the 70s showing that it had no different effects than placebo, it has become popular again nowadays especially in benign diseases[10]. However, its effectiveness remains a subject of debate and is not universally accepted or consistently validated. Several meticulously conducted randomized controlled trials have demonstrated no significant benefit from its use [11,12].

Many of the studies demonstrating the benefits of low-dose radiotherapy for osteoarthritis are often criticized for their weak design and methodology, as highlighted in systematic reviews[13]. Even those who advocate for the use of low-dose radiotherapy critique the current literature for its predominantly retrospective and non-standardized nature. Furthermore, there is a general acknowledgment of the absence of large randomized controlled studies, which could offer more conclusive evidence[14].

Systematic reviews revealed that most of the studies regarding low-dose radiotherapy are weakly designed and the probable cause of the positive results are due to regression to the mean effect and response to placebo[12-15]. There is even a randomized prospective sham-controlled blinded study supporting this assertion. In this study, standard doses were compared to a sham treatment (one-tenth of the effective dose) and no significant difference was observed in terms of pain relief and functional improvement[15].

Prolotherapy, Mesotherapy

Prolotherapy is the repeated injection of a sclerosing agent, often such as hypertonic dextrose at concentrations of 12.5% to 25%, into chronically painful areas. The mechanisms of action are not entirely clear. With this method, local tissue irritation is created, and inflammatory pathways are activated. As a result, it is thought that the release of growth factors increases, fibroblasts are activated, and thus tissue healing is accelerated. In vitro studies have shown that prolotherapy with hypertonic dextrose favors the deposition of collagen and metabolic activity of chondrocytes[16,17]. Multiple injections of up to 0.5 mL are made into the structures around the joint that are the source of pain. Generally, 4 to 6 sessions are recommended[16,17]. However, there are in vitro studies that did not find a significant increase in cell proliferation or inflammatory response with prolotherapy[18].

There is a scarcity of well-designed studies available on the topic. However, the limited research available suggests that the effects of prolotherapy may exceed those of a placebo, rendering it a potential option for patients who do not respond to conventional treatments. Positive outcomes lasting up to three months have been reported[19].

For gonarthrosis, both intra-articular and peri-articular injections have been investigated. Hypertonic dextrose injections are suggested to be more effective than serum physiologique, with peri-articular applications showing slightly superior results compared to intra-articular injections[20,21]. Its effectiveness was compared with other substances like corticosteroids, hyaluronic acid, ozone, and PRP, and mixed results have been reported[22-24].

In a comparative study between ozone and prolotherapy, no significant difference was observed [25]. Numerous studies have shown its short-term superiority over a placebo. However, most systematic reviews in the literature caution about the poor quality and high risk of bias present in the published clinical studies [21,23,24,26,27]. Until now, it is not considered a standard treatment for osteoarthritis in guidelines. Since no long-term side effects have been reported, it can be considered safe and can be recommended in selected patients.

Mesotherapy is an alternative medicine method originating from France. Despite the similarity of its name, it is unrelated to mesoderm in histogenesis. It is based on the belief that injection of various enzymes, vitamins, hormones, and local anesthetics into the middle of the skin layer or just below it is beneficial. Originally intended to alleviate pain, it is now predominantly employed for addressing dermatological problems[28].

For musculoskeletal pain, this therapy involves injecting NSAIDs, sterile water, or local anesthetic into the subcutaneous tissue at 5 to 20 different points in the affected area, typically without the use of steroids. Each injection point receives 0.1 to 0.2 mL. It has been reported that it can be applied from a single session

to 9 sessions[29,30]. While systematic reviews highlight the lack of standardization and heterogeneity in studies concerning its use, it is generally considered safe, well-tolerated, and effective[31].

The efficacy of subcutaneous injections in alleviating pain originating from deep tissues is a matter of question. Sterile water is unlikely to yield a discernible effect, and local anesthetics may only offer temporary skin anesthesia lasting a few hours. While subcutaneous NSAID application may offer relief comparable to topical analgesic ointments, the rationale for utilizing injections for this purpose warrants scrutiny.

Ozone

Ozone (O3) is a molecule containing three oxygen atoms, formed in nature as a result of exposure of oxygen to high-energy electric current and ultraviolet rays. It exists as a gas at room temperature. It is colorless and has a characteristic odor, and its name comes from the Latin word ozein, which means odorous, reflecting its characteristic smell. Ozone is an extremely unstable molecule and quickly turns into oxygen. It has strong oxidative potential and may secondarily induce antioxidant responses. It was previously used as a disinfectant in industry, and then it was tried locally on infected wounds to benefit from this effect. In some level 5 studies, it is claimed that ozone primarily increases oxygen radicals in the body due to its strong oxidative effect, and in turn activates antioxidant enzymes, thus creating an antioxidative effect and reducing the release of cytokines and free radicals [32]. Animal studies have found that injecting ozone directly into the joint reduces levels of TNF-α, IL-1β, and IL-6 without causing cartilage damage. It also lowers the expression of matrix metalloproteinase and bone morphogenetic protein [33]. There are studies showing that 4 to 8 sessions of ozone application into the knee in gonarthrosis significantly reduces pain at the end of the session, but its effect is short-lived and decreases within a few months [32,33]. In a study comparing ozone, PRP and hyaluronic acid, it was shown that the pain-relieving effect of ozone disappeared by the 6th month and PRP was superior in this regard [34]. It is important to note that inhalation of this substance can be toxic, and its use is contraindicated in certain conditions such as pregnancy, alcoholism, and hyperthyroidism. Despite these precautions, no serious side effects have been reported following its use. Due to its affordability and safety profile, it may be considered for patients upon request. While its effects have been reported in a few well-planned studies, it is crucial to acknowledge that systematic reviews indicate a majority of the studies were of poor quality and subject to bias [35].

Apitherapy, Hirudotherapy

Bees and Leeches are used in these treatments, which come from the names Apis and Hirudo. Apitherapy typically entails stinging the painful area one or more times, while hirudotherapy involves attaching a leech to the relevant area.

The hirudin substance, produced by leeches, possesses anticoagulant, thrombolytic, and somewhat anti-inflammatory properties, potentially generating both local and systemic effects by enhancing tissue perfusion. Advocates suggest that these effects could be advantageous in relieving joint pain. However, systematic reviews indicate that while osteoarthritis patients may experience benefits from leech therapy, caution is advised due to concerns regarding publication bias and the inherent limitations of the studies available [36]. Medical leeches, not cultivated in public pools and specifically bred for therapeutic purposes, appear to be safe when used once for each patient. However, the risk of infection should be kept in mind. Also, hemarthrosis after a leech therapy has been reported[37].

Bee venom is believed to influence healing by initiating certain neuro-inflammatory processes in the surrounding tissues, thereby reducing pain perception. It is suggested that the effects of bee venom largely occur through the activation of opioid and adrenergic receptors. While its primary applications are in circulatory disorders and inflammatory diseases, it has also been reported to be used for joint pain. Individuals with bee allergy should be identified carefully; anaphylactic side effects that may result in death have been reported[38].

The use of bee venom via bee sting is not considered the optimal therapeutic approach due to its association with severe adverse reactions, including soft tissue infection or renal failure. Therefore, the preferred method is administering adjusted doses through acupuncture[39]. There are studies indicating that bee venom

acupuncture significantly reduces pain and stiffness in patients with knee osteoarthritis. However, it's important to note that the majority of studies included in the analysis were evaluated as having a high risk of bias methodologically[40].

Acupuncture, Reflexology, Hijamat, Cupping

Acupuncture, a component of traditional Chinese medicine, is based on the concept of an energy flow within an individual. It posits that this flow is disrupted by illness, and the practitioner traditionally corrects it by inserting needles or by stimulating specific points on the body with laser or electric current. In certain Far Eastern countries, acupuncture treatment is covered by health insurance. It is claimed to have various effects, including pain relief, sedation, mood enhancement, immune system strengthening, regulation of homeostasis, regeneration enhancement, improvement in digestion, and immunomodulation.

Reflexology is also a method within traditional Chinese medicine where the body's energy flow is mapped onto the feet. It is believed that when energy flow is obstructed, manual intervention is required to open it. Practitioners assert that by applying pressure and massage to specific energy points on the feet, they can influence the functioning of internal organs. The points on the sole of the foot, representing various organs such as the thyroid, pancreas, kidney, and esophagus, are manipulated through squeezing, caressing, and stroking in diverse ways to promote healing.

Hijamat is an ancient type of treatment performed with or without cupping, with the aim of cleansing excessive blood, increasing blood flow and relieving pain in the relevant area. There are studies showing that cupping is especially effective in spasm-related muscle pain[41,42]

These practices belong to the empirical realm of traditional medicine. Rational levels of scientific evidence are absent or very weak[43,44]. Most of the studies that report positive results have poor methodological quality [45]. A small analgesic effect of acupuncture was found, which seems to lack clinical relevance and cannot be clearly distinguished from bias[46]. Six reviews, which included randomized, double-blind studies, have yielded substantial evidence indicating no discernible benefit. Studies advocating for the effectiveness of acupuncture frequently display bias and lack robust evidence to support its efficacy for any indication [43]. Placebo effects might be more pronounced in individuals who believe in them [47]. When proper hygiene standards are maintained, these treatments usually pose no harm.

Phytotherapy, Aromatherapy, Herbalism

Plants have been used for therapeutic purposes in every culture throughout history. In Türkiye, herbalists (Aktar) are indispensable pharmacies of traditional medicine.

The herbalist is familiar with the therapeutic properties of raw plants based on local teachings that are grounded in observations and utilizes this knowledge to craft medicines from the plants. Examples of the herbalist doctrine in traditional Turkish medicine include the belief that mint, and lemon are beneficial for the flu, while senna is effective for constipation[48].

In Türkiye phytotherapy is the most common method of alleviating pain in osteoarthritis patients[49].

With the development of modern pharmacy, the promising ones of these empirical treatments were scientifically examined and substances such as morphine, quinine, atropine, digoxin, and vincristine, which revolutionized medicine, were discovered. Pharmacognosy, a branch of science forming the foundation of modern pharmacy, delves into the examination of natural pharmaceutical raw materials and their chemical properties. Phytotherapy, within this scientific discipline, focuses on studying the therapeutic properties of plants. Aromatherapy, a subset of Phytotherapy, aims to harness the therapeutic benefits of various oil extracts obtained from plants through local application.

Winter cherry, willow, chrysanthemum oil, devil's claw, turmeric, currant seed, sesame oil, ginger, horsetail, nettle, rosehip, oxwort, comfrey and sanqi are commonly recommended by phytotherapists for alleviating joint pain[50,51].

Phytotherapists assert themselves as scientific herbalists; however, in practice, distinguishing them from traditional herbalists, who also lay claim to being phytotherapists, is not straightforward. Instances of quackery are also prevalent in the published literature (Figure 1), emphasizing the need for caution[52]. It's important to be aware that many phytotherapy products may not contain the claimed substance, some could have excessive toxic effects, and certain plants might induce drug interactions.

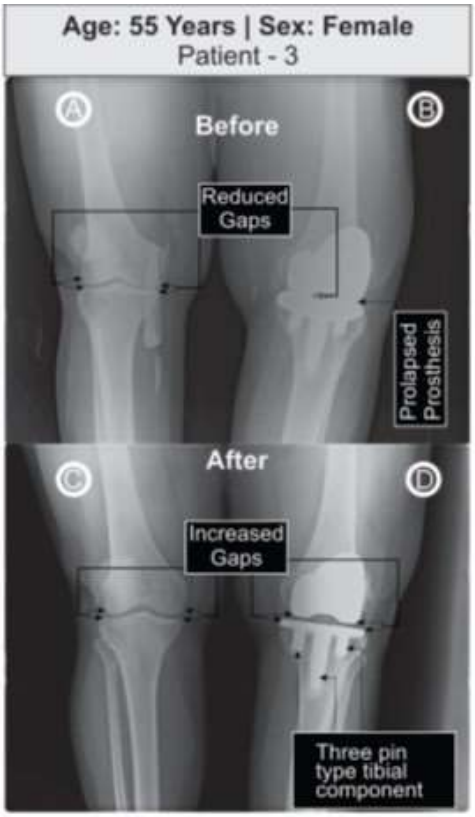


Figure 1. An example cited in a so-called scientific study ridiculously claims that phytotherapy led to an expansion of the joint space in a patient with a prolapsed knee prosthesis. However, the alleged "reduction in gaps" presented as evidence is simply a result of knee flexion.

For managing gonarthrosis pain, aromatherapy methods, which prioritize local effects over systemic effects and likely benefit from their application not from the oil itself but through massage, may be considered more suitable[53].

Homeopathy, Snake Oils

Homeopathy is an esoteric treatment method based on the belief that a disease can be treated by giving the patient very low doses of substances that would cause the symptoms of the disease in a healthy person [54]. Unlike classical medicine, which seeks to alleviate symptoms such as cough, fever, and pain, homeopathy embraces these symptoms as they are and avoids attempting to suppress them. It argues that the disease exists in another dimension. It claims to render certain disease-causing substances extremely diluted through the "potentialization" process, expose them to mechanical energies like shaking or jiggling, and assert that the resultant product is a form of medicine[55]. These substances are diluted to an extent that can be compared to throwing a sugar cube into the vastness of the Atlantic Ocean. The underlying claim is that the greater the dilution, the more potent the therapeutic effect becomes (Figure 2). Despite their significant dilution,

homeopathic drugs are often disproportionately more expensive than pharmacologically effective counterparts[56]. Proponents contend that shaking, representing a form of mechanical energy, impacts the outcome. The claim is that a sustained effect in homeopathy is typically attained with a single dose of medicine, proving beneficial for diverse physical problems, severe chronic diseases, and mental disorders[57,58].

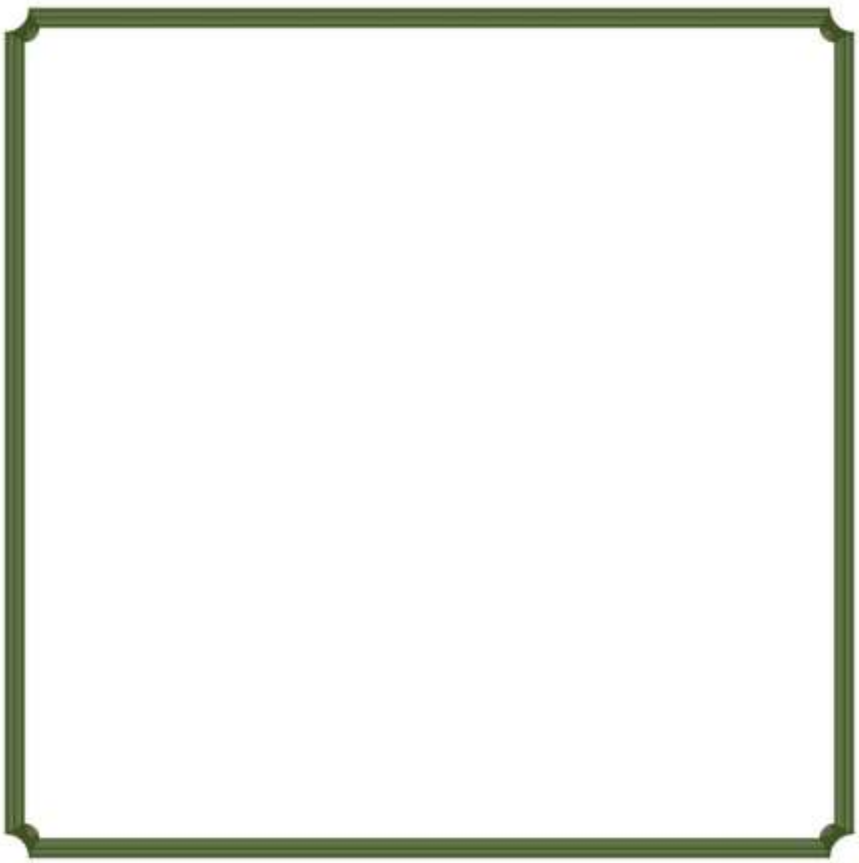


Figure 2.Example of homeopathic remedies:
a) Arnica remedy b) Calcarea phosphorica remedy c) Rhus toxicodendron remedy
The photo has been resized by a ratio of 1/10,000 for better visibility.

Undoubtedly, these claims bear no relation to scientific reality. Nevertheless, in Türkiye, homeopathy has been introduced as a course in certain pharmacy faculties, and even promoted through conferences within universities —an academic misstep comparable to offering astrology in an astronomy department. In very rare cases, if the patient's personality type is suitable for believing in such esoteric powers, it may be offered as a placebo. Ultimately, homeopathic medicines can have no effect, nor can they have side effects; As systematic reviews conclude that any given homeopathic remedy that leads to any effects more than placebo is not supported by any robust evidence[59,60]. Significant evidence of publication bias in favor of homeopathy has been well documented, and it is consistently shown that homeopathic medicine cannot be distinguished from the use of a placebo[60].

"Patent-Medicine" or "snake oil" are terms for non-drug commercial products extensively promoted with the claim that they cure various diseases. This phenomenon became prevalent in the last century, particularly in the United States. These products can take the form of potions, pills, ointments, jewelry, etc., and are frequently named after their inventor or marketer. They are heavily advertised as remedies for a range of related or unrelated diseases like kidney stones, erectile dysfunction, liver problems, clogged veins, etc. Despite having diverse contents, they typically lack an actual active ingredient for the claimed indications[61].

In conditions that cause chronic pain, such as gonarthrosis, patients may desperately seek help from these products. If present, active ingredient rates are generally low and do not cause any harm. However, it should be kept in mind that in cases where more than one drug is used in the elderly or individuals with other systemic diseases, serious side effects of the ingredients may occur.

These types of products are also available in Türkiye. Advertisements are typically broadcast on internet, satellite TV channels and marketed by telephone. Article 32 of Law No. 28886 dated 01.2014 and Article 19 of Law No. 1262 prohibit the sale and advertising of these products.

Conclusion

In Türkiye, the rate of people with chronic diseases applying alternative medicine methods is approximately 60% [49,62]. Patients often prefer these methods to relieve their pain. Nonsurgical treatment for gonarthrosis-related knee pain includes painkillers and life modifications. Weight loss, maintenance of muscle flexibility and strength through exercises, avoiding activities that strain the knee in daily life such as squatting, cross-legged, climbing stairs, and personalized painkillers are the basis of the treatment. In addition, massage and bandaging help reduce pain. A few days of spa vacation with plenty of hydration and heat can be beneficial for joint health[63]. If the patient is not satisfied after all those scientifically proven methods and requests more there is no harm in giving personalized recommendations. It's important to remember that the placebo effect can be a powerful painkiller, especially when its expensive or accompanied by a certain ritual [64-66]. The effectiveness of alternative treatments probably depends on this. Prolotherapy, which is based on intra-tissue substance injections, radiotherapy, and ozone therapy, which can modify the chemical balances within the body, stand out in terms of plausibility and their favorable safety profiles. Wet-Cupping and leech therapy around the joint will not be suitable due to the possibility of infection. Aromatherapy, combined with massage, can be beneficial for joint pain.

Acupuncture and reflexology are ancient Chinese medical practices; their teachings and alleged mechanisms of action have no basis in reality. Likewise, homeopathy stands out as a ridiculous example of quackery. One should stay away from cure-all drugs that are marketed with excessive advertising and make extravagant promises.

When recommending methods to patients in a realm where truth and lies intertwine, physicians must first consult their own conscience. Alongside the application of scientific knowledge with the most appropriate techniques, the practice of medicine also demands human skills like reassuring the patient, protecting their peace of mind, and easing their concerns. Alternative medicine may have a place only within these narrow functions of medical art, and always in conjunction with authentic, evidence-based treatments.

References

1. Alternative medicine. Wikipedia. February 20, 2024. Accessed March 6, 2024. https://en.wikipedia.org/wiki/Alternative_medicine.
2. Wang WY, Zhou H, Wang YF, Sang BS, Liu L. Current policies and measures on the development of traditional chinese medicine in china. Pharmacological Research. 2021;163:105187.
3. Tıbbi Deontoloji Nizamnamesi (1960, 19 Şubat). Resmî Gazete (Karar No: 12578, Sayı: 10436). https://www.resmigazete.gov.tr/arsiv/10436.pdf.
4. Dove APH, Cmelak A, Darrow K et al. The use of low-dose radiation therapy in osteoarthritis: a review. International Journal of Radiation Oncology*Biology*Physics. 2022;114(2):203-20.
5. Hautmann MG, Rechner P, Neumaier U et al. Radiotherapy for osteoarthritis—an analysis of 295 joints treated with a linear accelerator. Strahlenther Onkol. 2020;196:715-24.
6. Álvarez B, Montero Á, Aramburu F et al. Radiotherapy for ostheoarticular degenerative disorders: When nothing else works. Osteoarthritis and Cartilage Open. 2020;1:3-4.
7. Mücke R, Seegenschmiedt MH, Heyd R et al. [Radiotherapy in painful gonarthrosis. Results of a national patterns-of-care study]. Strahlenther Onkol. 2010;186:7-17.
8. Keller S, Müller K, Kortmann RD et al. Efficacy of low-dose radiotherapy in painful gonarthritis: experiences from a retrospective East German bicenter study. Radiat Oncol. 2013;8:29.
9. Micke O, Ugrak E, Bartmann S et al. Radiotherapy for calcaneodynia, achillodynia, painful gonarthrosis, bursitis trochanterica, and painful shoulder syndrome - Early and late results of a prospective clinical quality assessment. Radiat Oncol. 2018;13:71.
10. Montero A, Sabater S, Rödel F, et al. Is it time to redefine the role of low-dose radiotherapy for benign disease? Ann Rheum Dis. 2020;79:e34-e34.

11. Mahler EAM, Minten MJ, Leseman-Hoogenboom MM et al. Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: a randomised, double-blinded, sham-controlled trial. Ann Rheum Dis. Published online October 26, 2018:annrheumdis. 2018-214104.
12. van den Ende CHM, Minten MJM, Leseman-Hoogenboom MM et al. Long-term efficacy of low-dose radiation therapy on symptoms in patients with knee and hand osteoarthritis: follow-up results of two parallel randomised, sham-controlled trials. The Lancet Rheumatology. 2020;2:e42-e49.
13. Minten MJM, Mahler E, den Broeder AA, Leer JWH, van den Ende CH. The efficacy and safety of low-dose radiotherapy on pain and functioning in patients with osteoarthritis: a systematic review. Rheumatol Int. 2016;36:133-42.
14. Weissmann T, Rückert M, Putz F, et al. Low-dose radiotherapy of osteoarthritis: from biological findings to clinical effects—challenges for future studies. Strahlenther Onkol. 2023;199:1164-72.
15. Niewald M, Moumeniahangar S, Müller LN et al. ArthroRad trial: randomized multicenter single-blinded trial on the effect of low-dose radiotherapy for painful osteoarthritis final results after 12-month follow-up. Strahlenther Onkol. 2024;200:134-42.
16. Arias-Vázquez PI. Intra-articular injections for treating knee osteoarthritis: a classification according to their mechanism of action. J Clin Rheumatol. Published online April 10, 2024.
17. Rabago D, Slattengren A, Zgierska A. Prolotherapy in primary care practice. Prim Care. 2010;37:65-80.
18. Sells P, Vayster A, Hinkelman A et al. The efficacy of phenol-glucose-glycerin mixtures as a prolotherapy proliferative substance on fibroblast tissue culture. The Journal of Pain. 2024;25:22.
19. Vomer RP, Larick RS, Milon R, York E. The effect of intra-articular hypertonic dextrose prolotherapy on pain, quality of life, and functional outcomes scores in patients with knee osteoarthritis. Cureus. Published online November 1, 2023.
20. Avşar MT, Okudan RN, Gümüş ZZ, Samancï R. Efficacy of prolotherapy with periarticular 5% dextrose in the treatment of knee joint osteoarthritis. International Journal of Traditional and Complementary Medicine Research. 2021;2:162-66.
21. Sit RW, Chung VCh, Reeves KD, et al. Hypertonic dextrose injections (prolotherapy) in the treatment of symptomatic knee osteoarthritis: A systematic review and meta-analysis. Sci Rep. 2016;6:252-47.
22. Bae G, Kim S, Lee S, Lee WY, Lim Y. Prolotherapy for the patients with chronic musculoskeletal pain: systematic review and meta-analysis. Anesth Pain Med. 2021;16:81-95.
23. Hassan F, Trebinjac S, Murrell WD, Maffulli N. The effectiveness of prolotherapy in treating knee osteoarthritis in adults: a systematic review. Br Med Bull. 2017;122:91-108.
24. Wee TC, Neo EJR, Tan YL. Dextrose prolotherapy in knee osteoarthritis: A systematic review and meta-analysis. Journal of Clinical Orthopaedics and Trauma. 2021;19:108-117.
25. Hashemi M, Jalili P, Mennati S et al. The Effects of Prolotherapy With Hypertonic Dextrose Versus Prolozone (Intraarticular Oone) in Patients With Knee Osteoarthritis. Anesth Pain Med. 2015;5(5).
26. Waluyo Y, Artika SR, Insani Nanda Wahyuni, Gunawan AMAK, Zainal ATF. Efficacy of prolotherapy for osteoarthritis: a systematic review. JRM. 2023;55:jrm00372.
27. Chen Y-W, Lin Y-N, Chen H-C, Liou T-H, Liao C-D, Huang S-W. Effectiveness, Compliance, and Safety of Dextrose Prolotherapy for Knee Osteoarthritis: A Meta-Analysis and Metaregression of Randomized Controlled Trials. Clinical Rehabilitation. 2022;36:740-52.
28. Hassan F, Murrell WD, Refalo A, Maffulli N. Alternatives to biologics in management of knee osteoarthritis: a systematic review. Sports Medicine and Arthroscopy Review. 2018;26:79-85.
29. Chen L, Li D, Zhong J, Qiu B, Wu X. Erratum to "Therapeutic Effectiveness and Safety of Mesotherapy in Patients with Osteoarthritis of the Knee". Evid Based Complement Alternat Med. 2018.
30. Mammucari M, Gatti A, Maggiori S, Sabato AF. Role of mesotherapy in musculoskeletal pain: opinions from the italian society of mesotherapy. Evid Based Complement Alternat Med. 2012;:43-69.
31. Faetani L, Ghizzoni D, Ammendolia A, Costantino C. Safety and efficacy of mesotherapy in musculoskeletal disorders: A systematic review of randomized controlled trials with meta-analysis. J Rehabil Med. 2021;53:jrm00182.
32. Lopes de jesus CC, Dos santos FC, De jesus LMOB, Monteiro I, Sant'ana MSSC, Trevisani VFM. Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: A randomized, double-blinded, placebo-controlled study. PLoS ONE. 2017;12(7).
33. Akcali, D., İnan, N., Vurallı, D., Dayanır, H., & Babacan, A. Gonartroz Hastalarında İntraartiküler Ozon Enjeksiyonunun Ağrıya Etkisi. Gazi Medical Journal, 2016;27(3).
34. Duymus TM, Mutlu S, Dernek B, Komur B, Aydogmus S, Kesiktas FN. Choice of intra-articular injection in treatment of knee osteoarthritis: platelet-rich plasma, hyaluronic acid or ozone options. Knee Surg Sports Traumatol Arthrosc. 2017;25:485-92.
35. Sconza C, Respizzi S, Virelli L, et al. Oxygen–ozone therapy for the treatment of knee osteoarthritis: a systematic review of randomized controlled trials. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2020;36:277-86.
36. Wang H, Zhang J, Chen L. The efficacy and safety of medical leech therapy for osteoarthritis of the knee: A meta-analysis of randomized controlled trials. International Journal of Surgery. 2018;54:53-61.
37. Curcio J, Lloyd CM. Leech me alone! Atraumatic hemarthrosis after hirudotherapy. Cureus. Published online February 7, 2020.
38. Park JH, Yim BK, Lee JH, Lee S, Kim TH. Risk associated with bee venom therapy: a systematic review and meta-analysis. PLoS ONE. 2015;10(5)
39. Jagua-Gualdrón A, Peña-Latorre JA, Fernadez-Bernal RE. Apitherapy for osteoarthritis: perspectives from basic research. Complement Med Res. 2020;27:184-92.
40. Gu JH, Kim E, Park YC, Jung IC, Lee EJ. A systematic review of bee venom acupuncture for knee osteoarthritis. J Korean Med Rehabil. 2017;27:47-60.
41. Mohamed AA, Zhang X, Jan YK. Evidence-based and adverse-effects analyses of cupping therapy in musculoskeletal and sports rehabilitation: A systematic and evidence-based review. *BMR*. 2023;36:3-19.

42. Azizkhani M, Ghorat F, Soroushzadeh SMA, Karimi M, Yekaninejad S. The effect of cupping therapy on non-specific neck pain: a systematic review and meta-analysis. Iran Red Crescent Med J. 2017;20(7).
43. Derry C, Derry S, McQuay H, Moore R. Systematic review of systematic reviews of acupuncture published 1996–2005. Clin Med. 2006;6:381-86.
44. Araya-Quintanilla F, Cuyúl-Vásquez I, Gutiérrez-Espinoza H. Does acupuncture provide pain relief in patients with osteoarthritis knee? An overview of systematic reviews. Journal of Bodywork and Movement Therapies. 2022;29:117-26.
45. Ezzo J, Berman B, Hadhazy VA, Jadad AR, Lao L, Singh BB. Is acupuncture effective for the treatment of chronic pain? A systematic review. Pain. 2000;86:217-25.
46. Madsen MV, Gotzsche PC, Hrobjartsson A. Acupuncture treatment for pain: systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. BMJ. 2009;338:a3115-a3115.
47. Kaptchuk TJ. Placebo effects in acupuncture. Medical Acupuncture. 2020;32:352-56.
48. Faydaoğlu, E., & Sürücüoğlu, M. S. Geçmişten Günümüze Tıbbi ve Aromatik Bitkilerin Kullanılması ve Ekonomik Önemi. Kastamonu University Journal of Forestry Faculty. 2011;11:52-67.
49. Külekçïoğlu S. Traditional and complementary medicine use for knee osteoarthritis. The European Research Journal. 2022;8:619-28.
50. Long L, Soeken K, Ernst E. Herbal medicines for the treatment of osteoarthritis: a systematic review. Rheumatology. 2001;40:779-93.
51. Dragos D, Gilca M, Gaman L et al. Phytomedicine in joint disorders. Nutrients. 2017;9:70.
52. Ganguly A. Topical Phytotherapy is the Nobel Approach for Revision of Total Knee Replacement: A Unique Case Study J Orthopedics Rheumatol. 2018;5:6.
53. Terzï A, Gebressalesie HT, Yildirim Y. Aromatherapy interventions in elderly person: a systematic review. J Tradit Complem Med. 2020;3:293-303.
54. Borkens Y, Endruscheit U, Lübbers CW. Homeopathy-A lively relic of the prescientific era. Wien Klin Wochenschr. 2024;136:177-84.
55. Smith K. Against homeopathy – a utilitarian perspective. Bioethics. 2012;26:398-409.
56. Leemhuis H, Seifert R. Prescriptions of homeopathic remedies at the expense of the German statutory health insurance from 1985 to 2021: scientific, legal and pharmacoeconomic analysis. Naunyn-Schmiedeberg's Arch Pharmacol. Published online March 2, 2024.
57. Shaw DM. Homeopathy is where the harm is: five unethical effects of funding unscientific 'remedies'. J Med Ethics. 2010;36:130-1.
58. Ernst E. A systematic review of systematic reviews of homeopathy. British Journal of Clinical Pharmacology. 2002;54:577-82.
59. Ernst E. Homeopathy: what does the "best" evidence tell us? Medical Journal of Australia. 2010;192:458-60.
60. Mathie RT, Ramparsad N, Legg LA, et al. Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis. Syst Rev. 2017;6:63.
61. Wikipedia the free encyclopedia. Patent medicine. Available at: https://en.wikipedia.org/wiki/Patent_medicine#Ingredients_and_their_uses. Accessed March 4, 2024.
62. Nural N, Çakmak S. Status of using complementary and alternative treatments of individuals with chronic disease. J Tradit Complem Med. 2018;1:1-9.
63. Forestier R, Erol Forestier FB, Francon A. Spa therapy and knee osteoarthritis: A systematic review. Annals of Physical and Rehabilitation Medicine. 2016;59:216-26.
64. Lee YS, Jung WM, Bingel U, Chae Y. The context of values in pain control: understanding the price effect in placebo analgesia. The Journal of Pain. 2020;21:781-89.
65. Kaptchuk TJ, Miller FG. Placebo effects in medicine. N Engl J Med. 2015;373:8-9.
66. Colloca L. The placebo effect in pain therapies. Annu Rev Pharmacol Toxicol. 2019;59:191-211.