

Terminalis - The enigmatic
Cranial Nerve 0 pg. 01

scary as it sounds? pg. 28

Obesity Drugs pg. 71

EDGE OF MEDICINE

SPRING 2024



TEAM

Editor in Chief - Rosa Tsucala

Deputy Editor in Chief - Albert Martin Garcia

Lead of Writers - Andreas Sarantopoulos

Co-Head of Editing - Elena Tzanetou

Co-Head of Editing - Anna Aggelaki

Lead of Design - Aphrodite Pascoe

Authors

Alexandros Kordatzakis

Lyssa Hadjikakou

Nastasios Villias

Anna Maina

Antonios Papasavvas

Charilaos Spanoudis

Christina Mastori Kourmpani

Mitria Skartadou

Elena Mystakidi

Eni Zouganeli

Ilias Zreiq

Rich Struecker

Ambriella Kavvadia

Caterina Tsilaki

Dagdalini Rigena Frangouli

Ikolaos Ziogas

Rosa Tsucala

Yama Abu Helou

Tavros Makos

Zena Al-Dakkak

Editors

Ahmed Al-Bunnia

Anna Angelaki

Burelien Szarf

Farooq Imtiaz

Christos-Rafail Karathanasis

Elena Tzanetou

Fatima Arifagic

Caline Skouros

arios Lampaditis

Huda Saleh-Bey-Kinj

Graphic Designers

Nastasia Lebedeva

Ambriella Kavvadia

Sara Alketbi

THIS ISSUE



European
University Cyprus

Dear Reader,

Welcome to the first edition of Edge of Medicine, the **student-led science journal** of the European University Cyprus. This publication is dedicated to presenting the **latest research findings** in the realm of **medical sciences**.

Our mission is to keep readers informed of the most **recent pioneering discoveries** and advancements across **various medical disciplines**. Join us on this journey of discovering ground breaking research.

We provide students the opportunity to experience the process of writing a publication through the **peer-review system** and **practice** their **scientific writing skills**.

In this issue you can explore articles within the **categories** of: **Neurology, Cardiology, Oncology, Gynecology, Radiology, Ophthalmology, Endocrinology, Immunology, and Sports Medicine**.

If you are interested in **joining us**, feel free to **email** us at edgeofmedicine.mag@gmail.com or through our **Instagram** account @edgeofmedicine.mag.

Yours sincerely,

A handwritten signature in black ink, appearing to read "Rosa Tsucala".

Rosa Tsucala
Editor in Chief
Bsc Biomedical Science
1st Year Medicine



NEUROLOGY 01

- Unraveling the Mystery: Nervus Terminalis - The enigmatic Cranial Nerve 0 01
Use of Angiography for Moyamoya Disease Diagnosis 05
Embracing Diversity in ADHD Treatment: Beyond Medication 08
Neurosurgical Considerations for Patients with Meningioma 14
A review of Multiple Sclerosis: diagnosis, clinical progression, pathogenesis, and treatment 19

CARDIOLOGY 24

- Mitral Valve Prolapse 24
Takotsubo Cardiomyopathy: Is it as scary as it sounds? 28

ONCOLOGY 33

- The Role of Metabolism on Cancer Pathogenesis: Why Genetics Is Not the Only Player 33
Leptomeningeal Carcinomatosis 37
Peto's Paradox 39

GYNECOLOGY 44

- Influenza Vaccination During Pregnancy: Is it safe? 44
Laparoscopy: an established alternative in gynecology 46

RADIOLOGY 61

- Treating Brain Tumours with Stereotactic Radiosurgery 61

OPHTHALMOLOGY 66

- Effects of UV Rays on the Human Eye 66

ENDOCRINOLOGY 71

- Unveiling the Efficacy of Anti-Obesity Drugs 71

IMMUNOLOGY 77

- Immune Checkpoint Inhibitors in HIV Infection. A potential therapeutic opportunity? 77

SPORTS MEDICINE 82

- Is it for you?: Impacts of a Ketogenic Diet on Sports Performance 82

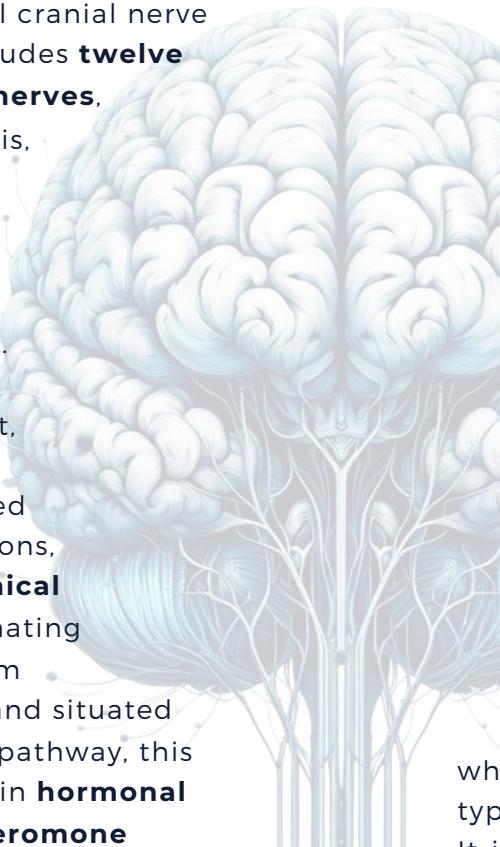
UNRAVELLING THE MYSTERY: NERVUS TERMINALIS - THE ENIGMATIC CRANIAL NERVE 0

WRITTEN BY ALEXANDROS KORDATZAKIS
EDITED BY AURELIEN SZARF
DESIGNED BY APHRODITE P. PASCOE

The traditional cranial nerve anatomy includes **twelve recognized nerves**, yet Nervus Terminalis, or **Cranial Nerve 0**, remains largely undocumented despite its **discovery over a century ago**. This article reviews its historical context, anatomical details, and the hypothesised physiological functions, emphasising its **clinical significance**. Originating embryologically from **neural crest cells** and situated along the olfactory pathway, this nerve is implicated in **hormonal regulation and pheromone detection**, potentially affecting reproductive and social behaviours. This article also highlights the **need for further research** to clarify its roles and develop therapeutic interventions for any associated neuroendocrine disorders.

INTRODUCTION

We are all familiar with the **12 traditional Cranial Nerves**, but few know that we actually have another one, called **nervus terminalis**, or **Cranial Nerve 0**. Despite its confirmed presence, knowledge about it remains **sparse** and its anatomy and function are mostly **undocumented** and poorly understood.

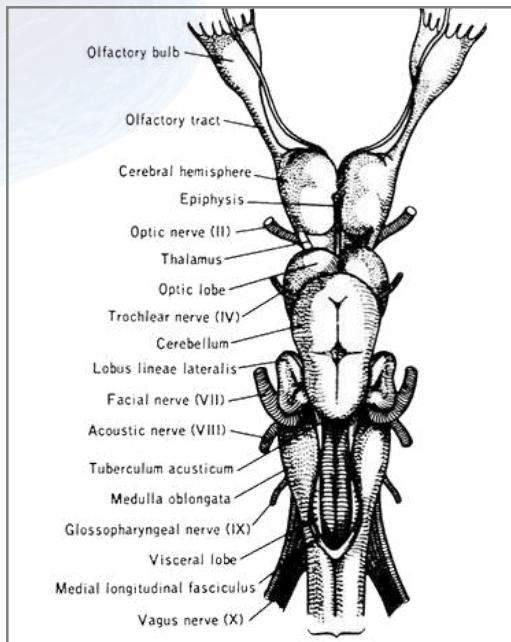


In this article, we aim to shed light on the Nervus Terminalis (NT), delving into its historical context, current understanding, ongoing research and its potential implications. Nervus Terminalis, often called the **Terminal Nerve**, Nerve Null, Cranial Nerve Zero "0", and **Cranial Nerve XIII/13**, was first identified in the human brain in **1913** [3]. Due to its extremely fine size and **delicate** nature, many scientists were accidentally while ~~dissecting~~ **researching** it with different types of tissue to expose the brain. It is notable that it is absent from medical literature, with most textbooks **continuing to overlook** it even today! [1]

ANATOMY

Nervus Terminalis is a **nerve bundle**, primarily composed of unmyelinated fibres in the ventral surface of the brain. It is a bilateral bundle that originates distinctly from the **neural crest**, separate from the olfactory nerve which arises from the nasal placode. It runs in the **subarachnoid space** from the medial olfactory stria on the inferior surface of the frontal lobe, medially to the olfactory nerve, across the surface of the **gyrus rectus**.

and through the cribriform plate to the **nasal septum** [4]. As the name suggests, this **paired nerve** extends into the forebrain's **lamina terminalis**, a thin layer of grey matter located above the optic chiasm and forming the medial sector of the rostral wall of the third ventricle [2].[Fig. 2]



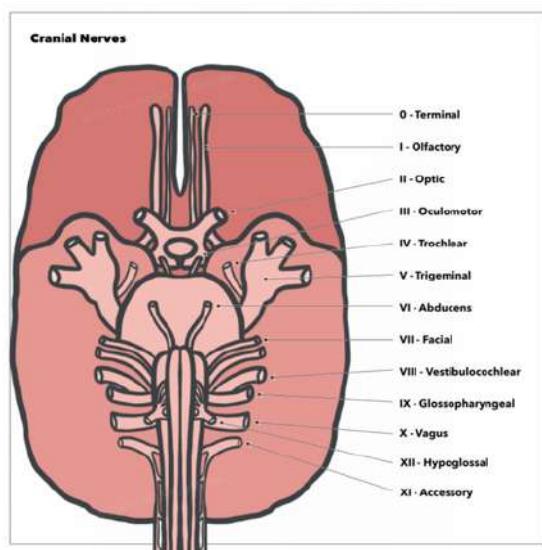
[Fig. 1] Illustration of the Cranial Nerves [13]

EMBRYOLOGY

The **development** of Nervus Terminalis is one of the most enigmatic events in the **formation of the cranial ganglia**. It originates embryologically from **neural crest cells** at the anterior limits of the **neural tube**, and it forms a complex interface with the differentiating **olfactory and adenohypophyseal placodes**. It then differentiates between tissue that gives rise to the embryonic olfactory placode and that which gives rise to the neural crest. [6][7]

Nervus Terminalis' cells **migrate from regions** close to or within the olfactory placode, with the result of this migration including cells containing neuroactive peptides such as **Gonadotropin-Releasing Hormone (GnRH)**, which is responsible for the release of **Follicle-Stimulating Hormone (FSH)** and **Luteinizing Hormone (LH)** from the anterior pituitary. This plays a pivotal role in the development and differentiation of the **Hypothalamic-Pituitary-Gonadal- (HPG) -axis**, but may also be potentially critical for the normal sexual development of both male and female patients [2] [Fig. 3].

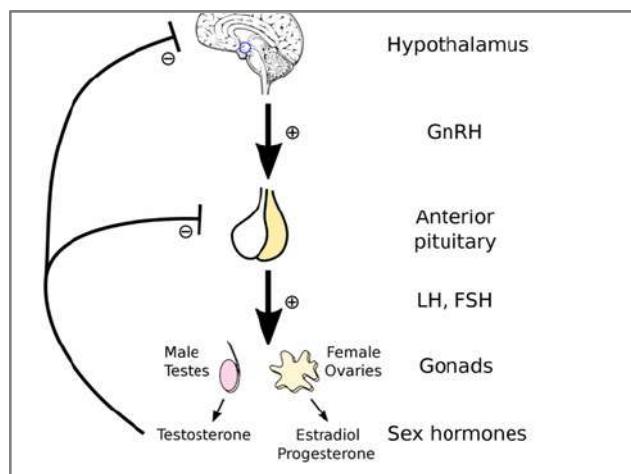
According to a 2022 study [8], one of the requirements for a fibre to qualify as a portion of the terminal nerve is that its cells must originate from the neural crest, yet migrate from the olfactory placode to frontal brain areas!



[Fig. 2] Illustration of the Cranial Nerves: CN0-CNXII. Illustration by Emma Gregory [5]

PHYSIOLOGY

Although its functions are **not fully understood**, NT is hypothesised to be involved in **hormonal regulation**, the **detection of pheromones**, and interacting with the Limbic System, suggesting a role in modulating reproductive and social behaviours.



[Fig. 3] The Hypothalamic–Pituitary–Gonadal axis [10]

As noted before, NT **contains fibres** that are **rich in neuroactive peptides** such as **GnRH**, which regulates gonadotropins such as **FSH** and **LH**. These hormones are vital for stimulating the synthesis and release of gonadal steroid hormones like **testosterone** and **estradiol**, essential for the development and function in both females and males. Finally, it has been suggested that this nerve may have **neuromodulatory implications** through GnRH and the nasal mucosa blood vessels and glands, which could exert regulatory functions of human sexual behaviours. [9]

Evidence suggests that the GnRH component of NT is neuromodulatory, exerting a level of **neurophysiological regulation** over the olfactory epithelium, thus making pheromones more readily detectable [6]. **Pheromones** are **chemical signals** that influence the behaviour and physiology of individuals, typically within the same species [11]. It would thus seem reasonable that the NT is releasing neuropeptides that presumably **enhance olfaction** in selected odours that affect reproductive behaviour and mate selection. [12]

The **axons of NT** sends fibres to the rostral ventral brain structures, primarily **limbic areas** (i.e., amygdala, hypothalamic nuclei) thereby potentiating the **development of the Hypothalamic-Pituitary-Gonadal axis**, and is involved in emotion, behaviour, and memory. Through these connections, the nerve could influence emotional responses to **social and sexual cues**, potentially impacting behaviours such as **mating and aggression**. [12]

CLINICAL SIGNIFICANCE

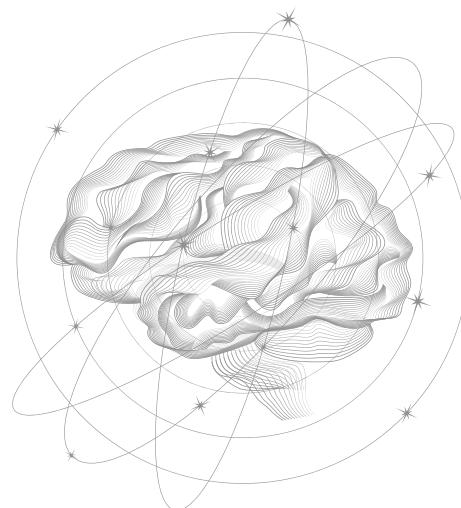
Due to its shared **migratory pattern** of hypothalamic GnRH neurons in the HPG-axis, **lack of basal forebrain GnRH cells** appears to be the primary cause of **hypogonadotropic hypogonadism**, associated with the genetic condition known as **Kallman's syndrome (KS)**, with the addition of varying degrees of olfactory dysfunction. [12]

KS is also associated with **primary amenorrhea** or failure to begin menstruation in women, resulting in **infertility, poorly defined secondary sexual characteristics** and, in some cases, **cleft palate, renal aplasia or agenesis, cryptorchidism, hearing deficits**, and other abnormalities, dependent upon the genes that are involved [2]. **Clinical studies** have revealed that losing function is the result of **point mutations and deletions** in the **kisspeptin 1 gene (KISS1)** [6], a gene associated with many functions of the Central Nervous System, primarily expressed in the hypothalamus, functioning as an essential gatekeeper of the **GnRH reproductive circuit** [6].

CONCLUSION

Nervus Terminalis, or Cranial Nerve 0/13, while often overlooked, is crucial for understanding several complex physiological and psychological processes. It has key roles in hormonal regulation, pheromone detection, and influencing emotional responses through its connections with the limbic system. These functions link the nerve closely to reproductive health and social behaviour, with implications for conditions like Kallman's syndrome and social communication disorders. The clinical relevance of the Nervus Terminalis is significant, offering potential new approaches for diagnosing and treating neuroendocrine disorders. Despite its importance, the small size and complex nature of the nerve makes it difficult to study and understand fully.

Future research should focus on developing better diagnostic tools to visualise and study this nerve more effectively. Medical and health sciences students will benefit from a better understanding of the basic science and clinical aspects associated with traditional cranial nerve teaching, along with the growing body of scientific evidence on NT.



REFERENCES



USE OF ANGIOGRAPHY FOR MOYAMOYA DISEASE DIAGNOSIS

WRITTEN BY ERICH STRUECKER
EDITED BY AURELIEN SZARF
DESIGNED BY APHRODITE P. PASCOE

Moyamoya disease is a **CNS** (Central Nervous System) **vascular disorder** which **occurs rarely**, particularly in the brain and has considerable problems in diagnosis and therapy. It's characterised by **narrowing or obstruction of the arteries of the brain**, which can result in strokes, haemorrhages and seizures in the patients affected by it, particularly in the **East Asian population**. Therapy can be achieved by either **medication** or **revascularization surgery**, which has proved **difficult in paediatric cases**. The diagnosis is dependent on neuroimaging. **Angiography** in particular is used to assess the disease's progression and severity. The **Suzuki Grading System (SGS)** is used coupled with angiography to make diagnosis easier. Finally, as more research is done in angiography and its uses, the quicker the diagnosis of Moyamoya will be in future cases.

Moyamoya disease is a **rare** vascular disease that targets the brain [1]. It was first described by **Takeuchi and Shimizu in 1957**, the term moyamoya was coined by Suzuki and Takaku in 1969 and is the **Japanese word for the phrase “puff of smoke,”** which describes the appearance of the small vasculature inside the brain as a result from the disease [1,2].



In normal physiology, the **carotid arteries** provide the brain with **oxygen-rich blood** from the lungs. In the case of moyamoya, the disease **causes the brain vasculature to narrow**, which causes the carotid arteries and the distal small arteries to become **obstructed or tangled** which will decrease the blood flow to the brain [1].

Patients with moyamoya can exhibit **seizures**, **epilepsies**, or **strokes**. They are usually prone to **brain hemorrhages**, involuntary jerky movements, and recurring ischemic attacks, among others. Moyamoya is usually diagnosed in **children aged ten to fourteen**, or in **adults in their 40s** [3]. Studies have also shown that moyamoya has an **“ethnic bias”** as it shows a prevalence in countries in East Asia, specifically **Japan and Korea** [4].

No cure has yet been discovered, so a lot of attention is placed on **diagnosis and treatments** that can be possible by improving the blood flow to the brain and controlling seizures [3].

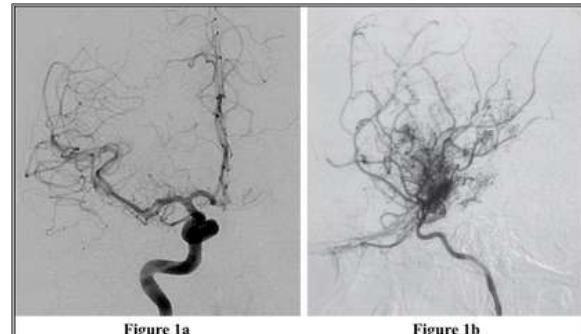
One possible treatment is **revascularization surgery**, which can help rebuild the brain's blood supply. This surgery can be divided into **direct and indirect revascularization** [5]. The direct procedure is characterized by artificially **creating an anastomosis** between the temporal and cerebral arteries of the head. This has, however, been shown to be **difficult for pediatric patients** with moyamoya disease. In the indirect procedure, blood-rich tissues, most often part of the **carotid artery**, are laid over the brain; this can cause **new blood-rich tissue** to be formed with the hope of improving blood flow [5].

Diagnosis is carried out by neurologists who order a series of imaging tests, such as **MRI**, **CT scans**, **MRA**, etc. As well as conducting **neurological examinations** in order to diagnose a patient with moyamoya [3].

Another way to help the diagnosis of moyamoya is **angiography**, which is a **type of x-ray** that is used to specifically look at **vasculature** [6]. **Blood vessels** usually **do not show up** in normal X-rays, and if they do, they are not clear enough for the doctors to be able to make a diagnosis, so in angiography a **special dye**, a contrast agent is injected to the patients blood to **make the vasculature visible** in a X-ray [6].

In the context of moyamoya, angiography is used to **diagnose and assess the severity** of moyamoya [7].

Criteria for the diagnosis using angiographic imaging were set in **1998**, including **stenosis**, or the occlusion, of the **intracranial internal carotid arteries** distally and the anterior or middle arteries proximally, among others [8].



[Fig. 1] Adapted from [10] left, shows a normal presentation of the right internal carotid artery in a cerebral angiogram and [11] right, narrowing of right internal carotid artery, indicative of moyamoya disease

When ordering an **angiogram**, doctors aim to **assess the quality of the brain's vasculature**, key diagnostic findings include the stenosis or occlusion of the terminal **internal carotid artery**, stenosis or occlusion of the **anterior and middle cerebral artery** [12]. Fig.1b shows severe narrowing of the distal internal carotid artery and of its distal branches [11].

Suzuki's grading system (SGS) was introduced in **1969** by **Suzuki and Takaku**, is still used today and is usually paired with angiographic imaging [13].

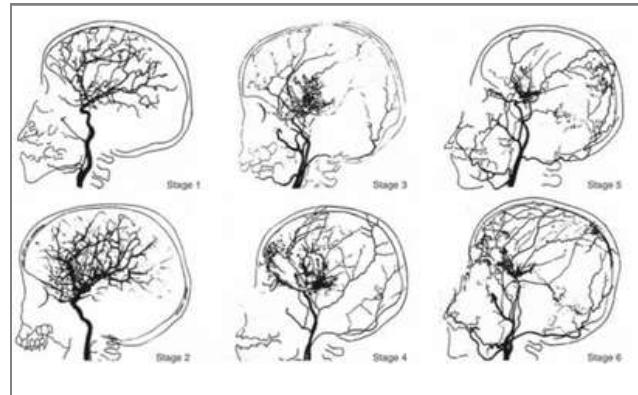
Grade	
Stage 1	Narrowing of carotid fork
Stage 2	Initiation of the moyamoya and dilatation of intracranial main arteries
Stage 3	Intensification of the moyamoya and defects of the ACA and MCA
Stage 4	Minimization of the moyamoya and defects of the PCA
Stage 5	Reduction of the moyamoya and development of ECA collaterals
Stage 6	Disappearance of the moyamoya and circulation only via ECA and VA

[Table. 1] Suzuki's Grading System for the degree of development of moyamoya vessels [11]

Although the **majority of patients** will advance through all the stages, it's still **helpful for physicians** to pinpoint the development of the disease.

Observing fig.1b in relation to fig.2 we can conclude that the patient of fig.1b is at **stage 3 of the SGS** [11]. This stage is named "**intensification of basal moyamoya**" and is characterized by the **obstruction of the anterior cerebral artery (ACA) and middle cerebral artery (MCA)** [14]. Stage 3 is subdivided into another three stages: partial non filling of ACA and MCA, partial preservation of ACA and MCA and finally the complete absence of ACA and MCA [14].

In conclusion, **angiography** is an important diagnostic tool in the evaluation of **moyamoya disease**. Since its establishment, it has **helped to determine the stenosis** or occlusion patterns of the **internal carotid artery and its branches**. It helps doctors not only gauge the severity, but gives them the opportunity to **see the vessels affected** and be able to create a better treatment plan for the patient afflicted with this disease.



[Fig. 2] Artistic depiction of Suzuki stages in Moyamoya disease in angiographic imaging [14]
Pediatric patients are more prone to cycle through the stages of the SGS, while adult patients will most likely remain fixed in one of the 6 stages [14].

REFERENCES





EMBRACING DIVERSITY IN

ADHD

TREATMENT

Beyond Medication

WRITTEN BY SAMA ABU HELOU
EDITED BY MARIOS LAMPADITIS
DESIGNED BY NOORA ALKETBI

Comprehending the complexities of attention-deficit/hyperactivity disorder (ADHD) is essential for a deeper and better understanding of it. In-depth discussions of ADHD's various symptoms, the impact of ADHD varies depending on gender and developmental stage, complex diagnostic processes, and available treatments are provided in this article. The article explores the underlying neurological mechanisms as well, including genetic predispositions and environmental factors. The article supports a comprehensive strategy for treating ADHD by integrating customized treatment plans and providing a thorough examination of behavioral and pharmaceutical therapies. Through the integration of scientific information with pragmatic ideas, this article seeks to enable clinicians and caregivers to effectively and compassionately navigate the problems presented by ADHD.

Understanding ADHD: What It is, Symptoms, and Diagnosis

Inattention, hyperactivity, and impulsivity are all various ways in which attention-deficit/hyperactivity disorder (ADHD) manifests. With normal childhood behaviors such as the inability to stay still and waiting for their turn being misrecognized as ADHD, it is essential to be aware of what it is and how it manifests; as these symptoms are not a result of an inability to understand a specific task or instructions (4). Keep in mind that the main difference lies in ADHD symptoms affecting daily functions and relationships. Noting that although there is a higher prevalence of ADHD in children, reaching 8.4%. Adults are also affected, with a percentage reaching 2.5%.

Moreover, the difference in symptoms' manifestation and presentation makes it easier for boys to be diagnosed than girls (1). Inattentive symptoms, such as forgetfulness, difficulty focusing, and difficulties with organizing, are often seen in girls. Symptoms of hyperactivity and impulsivity, such as blurting out or having trouble staying still in class, are more common in boys. While inattentive indicators are occasionally disregarded, hyperactive/impulsive symptoms are more readily observed by parents and educators.

Since girls frequently exhibit greater signs of anxiety, they are also less likely to receive an early diagnosis. Medical professionals may decide not to screen for ADHD in favor of treating a female patient's anxiety or depression. Complicating matters is the effect of hormones on anxiety and ADHD symptoms. Certain symptoms may seem to get worse with age or menstrual cycle irregularities, while other times they may seem to get better. These fluctuating symptoms may have an evident role in delaying the diagnosis.

With an onset before the age of 12, a 6-month period of persisting symptoms is required to establish an ADHD diagnosis. The symptoms are not to be limited to one setting but rather spread across multiple, such as home, school, work, and others. Presenting with a range of symptoms and presentations affecting focus, organization, impulsivity, and hyperactivity, ADHD has three types:

predominantly inattentive, predominantly hyperactive/impulsive, and combined presentation (1).

The inattentive type tends to affect and challenge focus, organization, as well as task completion. On the other hand, the hyperactive/impulsive type tends to cause excessive movement, impulsivity, and restlessness. The combined type would include the symptoms of the inattentive and hyperactive/impulsive types. The diagnosis of the inattentive type would focus on the likelihood and frequency of occurrence of the inability to pay attention to details, trouble following instructions, and forgetfulness. Moreover, the diagnosis criteria for the hyperactive/impulsive type include fidgeting, talking excessively, and difficulty waiting for one's turn (1).

A comprehensive and inclusive evaluation by a primary care provider, caregivers, teachers, and input from the patient themselves needs to be present to diagnose ADHD. The diagnosis is based on the completion of scales, questionnaires, and an evaluation of the medical and family histories. The process of diagnosis needs to be conducted and done thoroughly, and a comprehensive and inclusive psychiatric evaluation is needed as multiple conditions tend to mimic ADHD in presentation; those include learning disabilities and disorders, substance use, as well as mood disorders. Another reason is that ADHD might coexist and present with other conditions.

Moreover, the difference in symptoms' manifestation and presentation makes it easier for boys to be diagnosed than girls (1). Inattentive symptoms, such as forgetfulness, difficulty focusing, and difficulties with organizing, are often seen in girls. Symptoms of hyperactivity and impulsivity, such as blurting out or having trouble staying still in class, are more common in boys. While inattentive indicators are occasionally disregarded, hyperactive/impulsive symptoms are more readily observed by parents and educators.

Since girls frequently exhibit greater signs of anxiety, they are also less likely to receive an early diagnosis. Medical professionals may decide not to screen for ADHD in favor of treating a female patient's anxiety or depression. Complicating matters is the effect of hormones on anxiety and ADHD symptoms. Certain symptoms may seem to get worse with age or menstrual cycle irregularities, while other times they may seem to get better. These fluctuating symptoms may have an evident role in delaying the diagnosis.

With an onset before the age of 12, a 6-month period of persisting symptoms is required to establish an ADHD diagnosis. The symptoms are not to be limited to one setting but rather spread across multiple, such as home, school, work, and others. Presenting with a range of symptoms and presentations affecting focus, organization, impulsivity, and hyperactivity, ADHD has three types:

predominantly inattentive, predominantly hyperactive/impulsive, and combined presentation (1).

The inattentive type tends to affect and challenge focus, organization, as well as task completion. On the other hand, the hyperactive/impulsive type tends to cause excessive movement, impulsivity, and restlessness. The combined type would include the symptoms of the inattentive and hyperactive/impulsive types. The diagnosis of the inattentive type would focus on the likelihood and frequency of occurrence of the inability to pay attention to details, trouble following instructions, and forgetfulness. Moreover, the diagnosis criteria for the hyperactive/impulsive type include fidgeting, talking excessively, and difficulty waiting for one's turn (1).

A comprehensive and inclusive evaluation by a primary care provider, caregivers, teachers, and input from the patient themselves needs to be present to diagnose ADHD. The diagnosis is based on the completion of scales, questionnaires, and an evaluation of the medical and family histories. The process of diagnosis needs to be conducted and done thoroughly, and a comprehensive and inclusive psychiatric evaluation is needed as multiple conditions tend to mimic ADHD in presentation; those include learning disabilities and disorders, substance use, as well as mood disorders. Another reason is that ADHD might coexist and present with other conditions.

The actual and precise cause of ADHD remains unknown, despite extensive research. It is known by far that genetics play a vital role; however, no specific gene or gene sequence is suggested to be responsible for ADHD. Anatomically, it has been observed that those who have ADHD have reduced gray matter and white matter volume, in addition to having altered brain region activation during tasks. Other reasons might include prenatal exposure to toxins, low birth weight, and extreme stress during pregnancy.

ADHD Treatment: Pharmaceutical Approach

Medications prescribed for ADHD tend to focus on managing the symptoms of poor concentration, impulsivity, and hyperactivity instead of curing them.

Medications prescribed for ADHD include methylphenidate, lisdexamfetamine, dexamfetamine, atomoxetine, and guanfacine (2). Those medications come with side effects that include increased blood pressure, decreased appetite, trouble sleeping, and headaches (3).

Psychologists, counselors, and behavior therapists are among the qualified mental health practitioners who commonly provide behavioral treatment for ADHD. In order to reinforce similar strategies across many circumstances, it is frequently given in individual or group settings and may involve collaboration with parents, teachers, and other caregivers.

ADHD medications regulate focus, attention, and impulsiveness by targeting neurotransmitters. Stimulant medications mainly work on two neurotransmitters, norepinephrine, and dopamine, responsible for signaling in the brain. Those medications include methylphenidate, lisdexamfetamine, and dexamfetamine. Enhancing those neurotransmitters in areas of the brain responsible for attention and behavior regulation can improve concentration, and reduce hyperactivity and impulsivity (2).

Another type of ADHD medication is a selective norepinephrine reuptake inhibitor (SNRI). This type, which includes atomoxetine, works by blocking the reuptake of norepinephrine in the brain, leading to a prolonged effect. This mechanism helps mainly with concentration and controlling the impulsiveness (2).

Stimulating alpha-2 adrenergic receptors in the brain with medications such as guanfacine will help regulate attention and impulse control (2).

Several body parts are affected by ADHD medications, especially those containing methylphenidate (MPH) and amphetamines (AMP), each in a different way. Although they might cause a mild blood pressure and heart rate elevation that is not significant, in patients with pre-existing cardiovascular conditions, regular monitoring and caution are necessary.

On one hand, MPH usage showed no significant relationship with inducing anxiety or irritability. It was also suggested that long-term use of MPH reduces depressive symptoms and suicidal tendencies. On the other hand, AMP use is associated with a higher risk of psychotic episodes, which require further attention and caution. Additionally, gastrointestinal symptoms are noticed due to its decreased motility and increased gastric acid production, leading to nausea, constipation, stomach pain, and reduced appetite. Nonetheless, mild cases of dry eyes, blurred vision, and changes in the intraocular pressure were detected. For a better understanding of the long-term effects, which tend to be influenced by multiple factors such as dose and time, continuous monitoring is essential. (6)

As the mechanism of action of ADHD medications, especially amphetamines, works on increasing the levels of dopamine in the brain, which is responsible for the creation of a rewarding and reinforcing effect, substance abuse is a suggested side effect. The likelihood increases if the individual has a predisposition to substance abuse.

Based on individual needs and taking into account factors such as the severity of symptoms, age, medical history, and potential side effects, ADHD medications are prescribed. Despite the medications successfully managing and regulating the symptoms, it is crucial to monitor the effects and adjust the treatment when needed regularly. For a better-personalized

treatment plan, a holistic approach combining non-pharmaceutical lines of action such as behavioral therapy, counseling, and lifestyle modifications would help in addressing the unique needs and preferences of each individual with ADHD.

ADHD Treatment: Beyond Medication

A thorough treatment plan for people with ADHD must include behavioral therapy. While impulsivity, hyperactivity, and inattention can be effectively managed with medication, underlying behavioral patterns and the development of long-term coping skills are facilitated by behavioral therapy.

The goal of behavioral treatment for ADHD is to change behavior using a variety of methods, such as:

1. Parent Management Training (PMT): PMT gives parents the tools to adequately control their children's conduct at home and in social situations. PMT could entail establishing precise and unambiguous norms, putting incentives and sanctions in place, and encouraging constructive parent-child relationships.
2. Behavioral Interventions in Schools: School-based interventions aim to assist kids with ADHD in a learning atmosphere. Creating individualized education plans (IEPs) and offering accommodations such as preferred seating, extended time for exams and assignments, and teaching time and organization management.

3. Cognitive-Behavioral Therapy (CBT): CBT assists people with ADHD in recognizing and confronting maladaptive thought processes and building coping mechanisms to control impulsivity and enhance focus and attention spans. Additionally, it can treat co-occurring disorders like depression or anxiety, which frequently co-occur with ADHD.

4. Social Skills Training: Maintaining relationships and interacting with others are challenging tasks for many people with ADHD. To enhance social competence and peer interactions, social skills training imparts problem-solving strategies, perspective-taking, and communication abilities.

5. Mindfulness and Relaxation Techniques: Mindfulness exercises, including meditation and deep breathing, can help people with ADHD become more self-aware, better at controlling their emotions, and more focused and impulsive.

Psychologists, counselors, and behavior therapists are among the qualified mental health practitioners who commonly provide behavioral treatment for ADHD. In order to reinforce similar strategies across many circumstances, it is frequently given in individual or group settings and may involve collaboration with parents, teachers, and other caregivers.

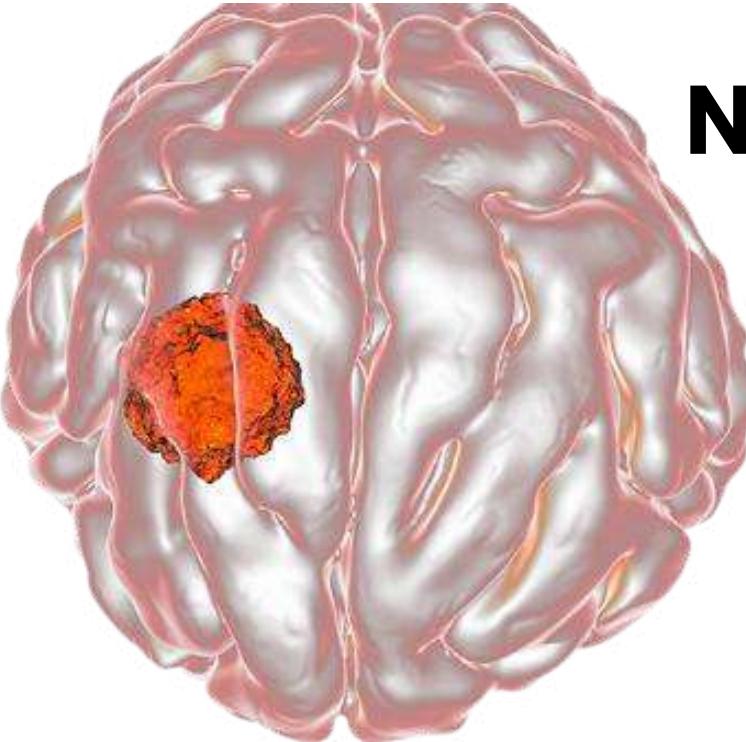
Research indicates that behavioral therapy can dramatically enhance social functioning, academic achievement, and symptoms of ADHD when used alone or in

conjunction with medication. Through the teaching of adaptive skills and the targeting of certain behaviors, behavioral therapy helps people with ADHD to control their condition better and thrive in a variety of living circumstances (5).

Ultimately, ADHD treatment ought to reflect the diversity of the patients it treats. We can ensure that everyone with ADHD gets the assistance they need to succeed by going beyond medicine and adopting a holistic approach that includes lifestyle modifications, counseling, and cultural awareness.

REFERENCES





Neurosurgical Considerations

FOR PATIENTS WITH

MENINGIOMA

WRITTEN BY STAVROS MAKOS

EDITED BY ELENI TZANETOU

DESIGNED BY NOORA ALKETBI

Meningioma is the most common primary tumor of the central nervous system. In recent decades pivotal advances have been achieved in the treatment of meningioma. Although most meningiomas are benign and have a good prognosis after surgery, physicians often face challenges when the tumor has complicated morphology, or it is adjacent to vital neuroanatomical structures. Nowadays, the gold standard treatment strategies of meningioma are mainly surgery and radiotherapy. In this work we summarize the key neuroanatomical and neurosurgical considerations that clinicians should adopt when managing a patient with meningioma and we urge clinicians to remain medically curious, adaptable and holistic when encountering complex and challenging patient cases.

Surgical management of Meningioma

Meningioma is the most common CNS tumor originating from arachnoid cap cells. In adults, 30% of primary intracranial tumors are meningiomas. The total incidence of meningiomas is estimated to be 83/100,000 and they demonstrate female sex, increasing age, and Caucasian race predilection [1,2,3].

An estimated 80-90% of meningiomas are benign and classified as WHO grade I. Routinely, these tumors are followed up for a long time or they are surgically excised and irradiated [1]. Atypical meningioma (WHO grade II) and anaplastic meningioma (WHO grade III) demonstrate poorer therapeutic results regardless of the treatment aggressiveness or variety used e.g. surgery, radiotherapy, and chemotherapy.

The primary treatment modality for symptomatic meningioma is surgical resection. The post operative goal is to relieve symptoms caused by the mass effect of the tumor, change the course of tumor progression, and provide the patient with a good quality of life. The neurosurgeon's clear indications to perform surgical resection of the meningioma include mass effect and increased intracranial pressure. The brain is a "closed box," and any increase in pressure causes compression of the brain parenchyma which might lead to brain herniation which is a fatal complication for patients. Surgical strategy is guided by an assessment of benefits and risks of the surgical procedure, histopathologic characteristics of tumors, tumor mass effect and clinical symptomatology, patients' preference, values, and beliefs. Surgical risk is assessed according to the patient's general condition, location, size, age, and symptomatology [3,4]. The location of the tumor is pivotal in determining surgical risk. Convex meningiomas can be resected with minimal if any complications and can be classified as low risk.

Full exposure of the surgical field, careful dissection of tumor capsule can protect the vascular bundle and lead to appropriate post operative results with reduced disability rates. Tumors localized in the olfactory sulcus, adjacent to the sagittal sinus, intraventricular, at the cerebellopontine angle, and falx cerebrum makes the excision more challenging and is classified as moderate risk. Meningiomas involving the dural sinus, vasculature, or cranial nerves pose a challenge to the operating surgeon.

High risk operations involve meningiomas originating from the clinoid process, cavernous sinus, and tuberculum sellae [5]. In the petroclival region there are important structures that converge such as cranial nerves, the cavernous segment of the internal carotid artery, basilar artery, superior cerebellar artery, and posterior cerebral artery. Tuberculum sellae meningiomas often involve the optic nerve and anterior cerebral artery. These structures wrap around the surface of the tumor and adhere to it.

When gross total resection is performed for meningiomas involving cortical veins or venous sinuses, damage to the venous circulation may occur. When the venous sinuses are partially unobstructed a subtotal resection can be performed [6].



Currently, clinical knowledge suggests that resection of the tumor should be performed outside the superior sagittal sinus. However, residual tumor may recur, and a choice between imaging follow-up or adjuvant radiosurgery should be made [7]. Tumors invading the superior sagittal sinus but without obstructing the lumen can be managed by resecting the tumor outside the venous sinus while the residual tumor in the sinus can be followed up at regular intervals. If the tumor is increasing in size during the follow up period, initial radiotherapy and subsequent surgical resection is recommended. In cases where the venous sinus is totally occluded, and the vein collateral circulation is established, surgical resection of the occluded venous sinus can follow while preserving the collateral vascular network during the surgery. Total removal of the invaded sinus is not dangerous and reconstructing the venous circulation is futile. Some neurosurgeons perform a reconstruction of the venous circulation to facilitate complete tumor removal.

Patients who might benefit from such an approach are those with affected venous compensation and with total occlusion of venous sinuses. Nonetheless, high quality evidence is lacking in the safety and efficacy of this approach. Injuring the unobstructed venous sinus might lead to devastating effects for the patients including cerebral infarction, intracerebral hemorrhage, loss of vision and infection.

Experience driven clinical knowledge supports the idea that removal of meningiomas invading the venous sinuses should not be the main goal of the operation.

Innovations in the field of neurosurgery such as surgical microscopy, neuronavigational technologies, intraoperative neurophysiological monitoring, intraoperative imaging, adaptive hybrid surgery and cavitation ultrasonic aspirators have increased operative success and decreased postoperative complications. When the meningioma is in the skull base the surgical intervention becomes challenging and plenty of these tumors cannot be completely excised regardless of which surgical methods and tools are used. Endonasal access allows the surgeon to reach deep into the ventral side of the base of the skull and safely resect the tumor (Class Simpson I resection) by avoiding damage to the brain parenchyma. Endonasal approach benefits patients with small meningiomas that are growing around and/or below the optic chiasm. However, endonasal approach should be avoided in patients with large-sized and asymmetric meningiomas and tumors surrounding major vessels and the optic nerves.

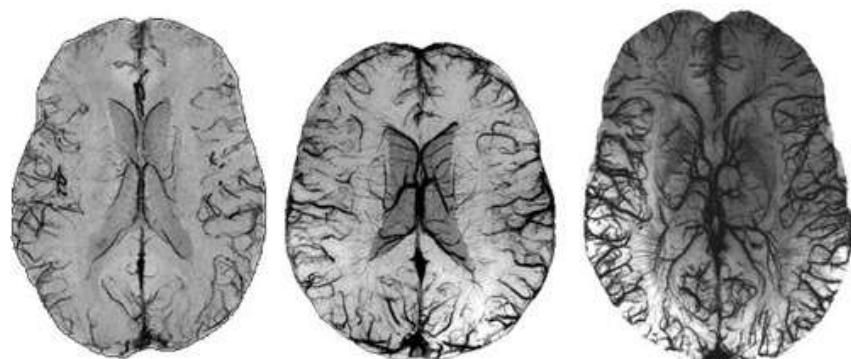


When tumors invade key anatomical positions, a narrow operating space increases the complexity of the operation and predisposes the patient to a greater risk of complications. Skull base meningiomas are mostly vascularized from the tumor's ventral vessels. The dura and the meningioma's surface vessels in the basal region can be exposed preferentially by an endonasal approach. There are two ways to endoscopically access the tumor, the Standard Endoscopic Endonasal Approach (SEEA) and the Expanded Endoscopic Endonasal Approach (EEEA). EEEA approach is preferred since surgeons do not pull on the brain parenchyma, do not damage the optic nerve, reduce congestion and edema of the brain while providing better cosmetic effects to the patient.

Skull base meningiomas that can be treated endoscopically include olfactory sulcus meningiomas, tuberculum sellae meningiomas, petroclival meningiomas and foramen magnum meningiomas. Major complications of endoscopic endonasal approach include cerebrospinal fluid leakage, infection, nerve injuries and vascular injuries [8].

Endoscopic endonasal approach should be the main choice for tuberculum sellae meningiomas with suspected involvement of the optic canal. Tuberculum sellae meningioma often grows into the optic canal through the medial edge of the cranial opening of the optic canal predisposing the patient to postoperative recurrence. A natural anatomical advantage exists for the endoscopic approach in tumors on the ventral side of the optic canal. However, appropriate evidence is lacking regarding whether transcranial or endoscopic endonasal approach provides better results for patients [9]. The main challenge of the endonasal approach that should not be overlooked involves reconstructing the skull base, especially for wide base meningiomas. Cerebrospinal fluid leakage is a quite common complication occurring in 30% of cases [10].

Surgeons should opt for a multilayer repair method of skull base reconstruction in comparison to a single layer repair method as a vascularized tissue patch provides greater results in comparison to a non-vascularized tissue patch.



The self-nasal septum mucosal flap with vascular pedicle is currently the best tool we possess at our disposal to meet the need of appropriate skull base reconstruction and reduce the risk of cerebrospinal fluid leakage to less than 5% [11]. Overall, the endonasal approach's efficacy is influenced by a multitude of factors such as the size, growth, and extension pattern, invasion degree and transfer status of the meningioma. Strict control of the indications and contraindications of endonasal approach impacts the surgery's prognosis. An example of an indication to perform the endoscopic endonasal approach is a small meningioma found in the midline anterior cranial fossa. This approach ameliorates the visual impairment caused by meningioma [12]. Nevertheless, when meningiomas are large, surrounded by blood vessels and calcified, endoscopic endonasal approach is not recommended [13].

Further contraindications for the endonasal approach include when the meningioma invades the medial side of the optic canal or when the

the tumor extends to the lateral part of the optic nerve. Furthermore, when the tumor involves the internal carotid artery, anterior cerebral artery, and anterior communicating artery an endonasal approach should not be adopted. It is important to note that the surgeon must have a clear field of vision, completely resect the lesion and avoid damage to key nerves and vascular structures. To achieve this, the skull base bone should be removed as much as possible to widen the operation channel. The surgeons experience excising complex tumors and surgical skills will play a crucial role during the operation.

Traditionally meningiomas are excised completely according to Simpson's classification of extent of resection. The surgeon tries to maintain intact the normal brain tissue adjacent to the tumor. Serious complications arise when the surgeon tries to completely excise tumors closely adherent to venous sinuses or neurovascular tissue of the cranial base [14,15]. Currently, subtotal resection is commonly used by surgeons to maintain intact venous structures and nerve function [16].

REFERENCES



A review of

MULTIPLE SCLEROSIS:

Pathogenesis, Diagnosis, Clinical Progression, and Treatment

Multiple sclerosis (MS) is an **immune-mediated** disease of the **central nervous system** with an age of onset between 20 to 40 years. Although the exact causes of MS are **unresolved** it most likely develops in genetically **predisposed** people as an abnormal reaction to **environmental** stimuli. The goal of the diagnosis is to document the progression of the disease over time and space by carefully examining the patient's medical history and performing clinical examinations. Although there is **no current cure**, there are several long-term, disease-modifying medications, symptomatic treatments, and corticosteroids for the management of relapses. This article discusses MS diagnosis and pathophysiology, with an emphasis on the available **treatment options**.

INTRODUCTION

Multiple sclerosis (MS) is one of the most common neurodegenerative autoimmune disorders, affecting about **2.8 million** people worldwide, with around 10,000-20,000 new cases diagnosed each year (2). Its age of onset is 18-50 years, peaking at 24 years and it appears that females are significantly more susceptible than males with a ratio higher than **3:1** (1). Although the exact cause of MS is unknown, it is thought to be an immune-mediated response to one or more

WRITTEN BY GABRIELLA KAVVADIA

EDITED BY ELENI TZANETOU

DESIGNED BY GABRIELLA KAVVADIA

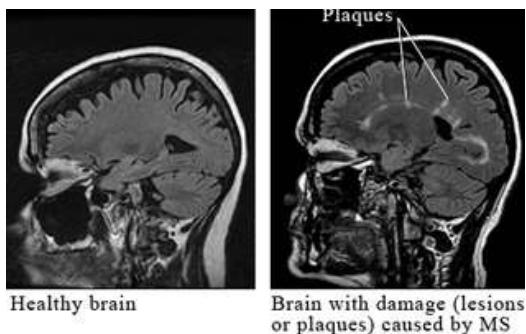
environmental triggers in a genetically susceptible individual. As an initial sign of the disease, young patients experience **acute relapses** and clinical symptoms which are often followed by a progressive form that can lead to permanent disability. As diagnostic procedures have evolved and signs and symptoms are visible with imaging methods, it is now possible to detect MS in its early stages, **minimizing** the activity of the **lesion** and preventing further **progression** of the disease with the appropriate treatment.



DIAGNOSIS

Multiple Sclerosis has a **variable clinical presentation** and yet there is **no specific definitive test**, making its diagnosis challenging, so a combination of **clinical examination** is needed in making an accurate diagnosis. The key components of evaluation along with medical history include an MRI, Evoked Potentials, Cerebrospinal Fluid (CSF) Analysis, blood test, and eye exam (3).

MRI is a diagnostic test that uses **large magnets** and a computer to make detailed **pictures** of organs and structures within the body **without** using **X-rays** and find plaques and certain pattern changes of brain tissue caused by MS (4).

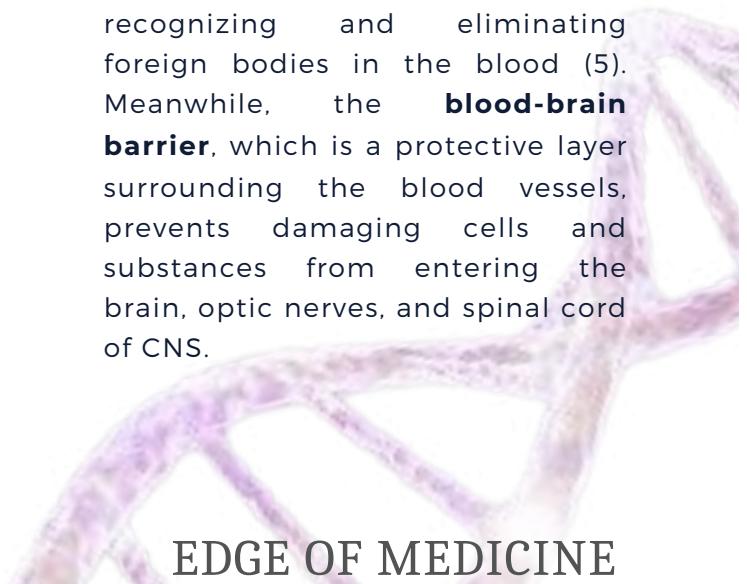


Evoked Potentials, on the other hand, record the brain's **electrical response** to visual, auditory, and sensory stimuli and identify **delays** in different brain areas which is a sign of MS. In addition, patients with MS produce **IgG antibodies** with an oligoclonal band pattern on electrophoresis, suggesting an inflammation in the body and an immune-mediated process within the CNS. This **elevation** of IgG antibodies can be assessed with a **Cerebrospinal Fluid Analysis** via a lumbar puncture.

Finally, people suspected of MS are recommended to have blood tests in order to rule out other causes of neurological symptoms such as B12 deficiency, Lyme disease or other autoimmune disorders and also have an eye examination to assess neurologic function. All these evaluations constitute the **McDonald criteria** or International Panel on Diagnosis of Multiple Sclerosis which provide guidance for MS diagnosis using both clinical characteristics and radiological evidence of disease activity.

IMMUNE SYSTEM INVOLVEMENT

In multiple sclerosis (MS), the immune system **mistakenly attacks** the **myelin sheath**, a protective covering that surrounds nerve fibers in the central nervous system (CNS), including the brain and spinal cord. This immune attack is primarily mediated by certain **malfuctioning immune cells** and molecules, leading to **inflammation**, **destruction of myelin**, and ultimately, **nerve fiber damage**. Specifically, white blood cells, such as lymphocytes and macrophages, protect the body by recognizing and eliminating foreign bodies in the blood (5). Meanwhile, the **blood-brain barrier**, which is a protective layer surrounding the blood vessels, prevents damaging cells and substances from entering the brain, optic nerves, and spinal cord of CNS.





In people with MS, however, the white blood cells and the blood-brain barrier are dysfunctional as a result of the entrance of damaging WBC and other molecules in the CNS and the false recognition of myelin as foreign and the attack of it. This causes inflammation along the nerves where the myelin is damaged and these areas of activity are referred to as lesions, or plaques. Damaged myelin can often be repaired by a procedure known as "**remyelination**" with the help of oligodendrocytes, but they may eventually disappear and become incapable of mending the damaged myelin.

TREATMENT

Although there **isn't a cure** for multiple sclerosis (MS), there are a number of treatments that can help **control** symptoms, **decrease** the disease's development, and **enhance** quality of life. These therapies include disease-modifying therapies (DMTs) to lower inflammation and relapses, symptomatic treatments to relieve particular symptoms, and rehabilitative therapies to improve physical function and mobility.

To begin with, **DMTs** function by altering the immune system's behaviour by **decreasing its likelihood to attack** the nerves in the CNS. This means decreased inflammation and **prevention from new relapses** and lesions to occur, as a result, they are considered to be highly **effective** in relapsing or active phase of MS.

There are several types of DMTs available for MS treatment such as Interferon Beta, Monoclonal Antibodies (mAbs) and Stem Cell Therapy each of which have a unique mechanism of action, method of administration, efficacy and safety profile (6). Betaseron, Extavia, Avonex, and Rebif are the four beta-interferon medicines that are currently on the market and their mechanism of action is to **bind** to specific **cell surface receptors**, express anti-inflammatory **cytokines** (eg, interleukin [IL] 4, IL-5, IL-10, IL-13, IL-27, and transforming growth factor beta) and **inhibit** the expression of proinflammatory cytokines (eg, IL-17, IFN γ , and tumor necrosis factor alpha). Thus they **stabilize** dysregulated CNS **inflammation** and indirectly **reduce neuronal demyelination**, preventing further neuronal damage. In an individual randomized, placebo-controlled trials, each IFN β product reduced annual relapse rates by around **30%–35%** and improved MRI and disability outcomes (7).

Another available treatment of DMTs is **Monoclonal Antibodies** Therapy which targets specific immune cells involved in MS via binding, blocking or signaling. The American Academy of Neurology (AAN) recommends **alemtuzumab** or **natalizumab** for patients in the relapsing-remitting phase who have highly active MS and ocrelizumab in patients with PPMS.

Results from phase III clinical trials demonstrated that natalizumab inhibits α4 integrins to block leukocyte migration across the blood, resulting in a reduction of 67% in clinical relapses and 83% in new brain MRI lesions. On the other hand, ocrelizumab, which binds through overlapping the epitope, is a recent addition on the market with results from the placebo-controlled clinical trial showing that it demonstrated reduction in CDP by 24% (6).

Finally, an emerging approach for patients with highly aggressive relapsing-remitting multiple sclerosis (MS) is **hematopoietic stem cell transplantation (aHSCT)**. The goal of it is to "reset" the immune system so that it will **no longer target the central nervous system**. This can be achieved by first eliminating the dangerous immune cells with chemotherapy and then a particular kind of stem cell, present in your bone marrow, is used to rebuild the immune system. It is a **one-time only** technique and retrospective clinical studies have further supported its effectiveness, showing potential advantages over conventional therapies in patients with cyclic recurrent MS (8).

While many people benefit from disease management medicines that lower disease activity and limit its progression, maintaining **symptom control** is ultimately what enables people to **live comfortably and safely**.

Symptom management can be achieved with corticosteroids (prednisone,

methylprednisolone) for acute exacerbations, muscle relaxants, and medication for fatigue and antidepressants (9). Nevertheless, drug therapies aren't solely the solution in treating MS. Lifestyle changes such as nutrient rich diet, daily exercise, and stress management combined with rehabilitation programmes can promote the individual's health (10). Rehabilitation can address problems with mobility, personal care, driving, as well as, difficulties in speech, swallowing, and brain function. Specifically, **physical therapy** enhances the person's strength, stability and gait while occupational therapy focuses on the person's independence, productivity, and safety regarding activities and employment.

CONCLUSION

In conclusion, multiple sclerosis necessitates a **holistic approach** to early diagnosis and therapy because it is a challenging and complicated condition with a distinct clinical presentation in each case. Fortunately, because of scientific advances, there are a number of effective treatments for multiple sclerosis that extend survival time, reduce relapses, and improve quality of life. These breakthroughs, especially when combined with ongoing research efforts, gives hope for even more groundbreaking discoveries in the near future.

REFERENCES





WRITERS

EDITORS

DESIGNERS

**LAUNCH
YOUR
FUTURE,
with every
edition!**

***JOIN OUR
TEAM!***

This is where curiosity meets science, join our team today and write the next chapter of medical innovation!

**JOIN EUC MEDICAL
SCHOOLS' FIRST
STUDENT-RUN
MEDICAL JOURNAL.**

[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

Mitral Valve Prolapse

WRITTEN BY ELENA MYSTAKIDI

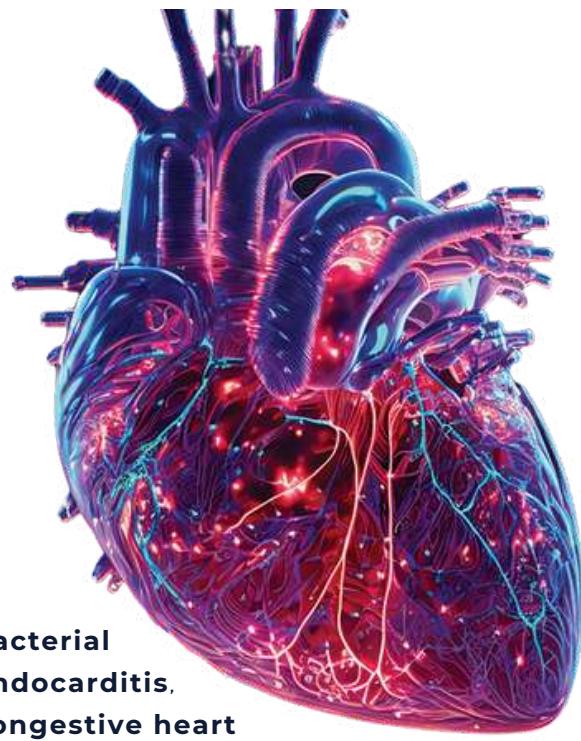
EDITED BY AHMED AL-BUNNIA

DESIGNED BY NOORA ALKETBI

Mitral valve prolapse (MVP), also known as Barlow syndrome, billowing mitral valve syndrome, click-murmur syndrome, floppy valve syndrome, mitral prolapse, and myxomatous mitral valve disease, is a **valvular heart disease**. It is most commonly a **benign condition**, and only in rare cases does it present with **life-threatening events**.

EPIDEMIOLOGY

Mitral valve prolapse (MVP) affects around **3% of the general population**, rendering it a relatively **common disorder**. It may have a primary or a secondary form. The primary form of MVP is characterized by **myxomatous degeneration**, without any underlying connective tissue issues. Secondary MVP, on the other hand, can have multiple causes, including **Ehler-Danlos syndrome, Marfan syndrome, polycystic kidney disease, graves' disease, and pectus excavatum**. For instance, Marfan syndrome patients have a notably high prevalence of MVP, at 91%. MVP can lead to significant complications such as **mitral valve regurgitation** (4%),



bacterial endocarditis, congestive heart failure and in severe cases with other comorbidities, **sudden death**. [1]

PATOPHYSIOLOGY

MVP refers to the **primary myxomatous degeneration** affecting one or both leaflets of the mitral valve. The primary myxomatous degeneration is a **non-inflammatory progressive dysfunction** of the valve caused by a defect in the mechanical integrity of the leaflet. This **degeneration** can manifest as various abnormalities, including **issues with the valve leaflets**, weakening and elongation of the **chordae tendineae**, dilation of the **mitral annulus**, or thickening of leaflet tissue, resulting in **segmental prolapse of the mitral leaflets**. [5] Disruption of the endothelium can lead to complications such as **infectious endocarditis** and **thromboembolism**. The degree of the structural derangement of the valve determines the severity of the disease and the **potential complications** that may present.

While most individuals with MVP exhibit **minimal structural derangement** of the mitral valve, which often presents with minimal clinical symptoms but can lead to complications in some cases, there is often **significant redundancy of the mitral valve leaflets**. This redundancy, by impairing the coaptation of the leaflets during systole, results in **mitral insufficiency**. Histologically, MVP is characterized by myxomatous degeneration or a connective tissue disorder. The **spongiosa** of the mitral valve leaflets **proliferates** with deposits of **mucopolysaccharides**, which have excessive **water content**, leading to **leaflet thickening**. There is also an increase in **type III collagen content**, along with fragmentation of elastin fibers. [2]

PHYSICAL EXAMINATION

MVP can manifest itself without symptoms, but it can also present with symptoms such as **atypical chest pain**, **palpitations**, **exertional dyspnea**, and **exercise intolerance**. The presence of signs and symptoms of mitral valve prolapse is typically correlated with the degree of blood regurgitation through the valve. Additionally, symptoms like **anxiety**, **low blood pressure**, and **syncope** may indicate dysfunction in the autonomic nervous system. Occasionally, supraventricular arrhythmias may occur, suggesting an elevated parasympathetic tone. Regarding auscultation during physical examination, in patients with MVP, a mid-systolic k followed by a late systolic murmur is often heard, typically loudest at the apex

The variation in the intensity of the **mitral valve murmur** in mitral valve prolapse depending on the **patient's position** is due to changes in the **volume of blood** returning to the heart and alterations in **intrathoracic pressure**. When a person stands or performs the **Valsalva maneuver**, venous return to the heart decreases. This reduction in venous return **decreases the left ventricular blood volume**, causing the prolapsed mitral valve leaflets to move further back **into the left atrium during systole**. This results in a more pronounced mitral valve prolapse and regurgitation, leading to a **louder murmur**. Conversely, when a person **squats**, venous return to the heart increases due to **decreased intrathoracic pressure**. This increased venous return results in **more blood in the left ventricle**, which can help prevent the prolapsed mitral valve leaflets from moving as far back into the left atrium during systole. As a result, the severity of mitral valve prolapse and regurgitation is reduced, leading to a **softer murmur**. Over time, it has been observed that individuals with MVP may develop a **spectrum of autonomic symptoms**, including panic attacks, anxiety, exercise intolerance, palpitations, fatigue, atypical chest discomfort, orthostatic issues, mood changes, and syncope. [3]

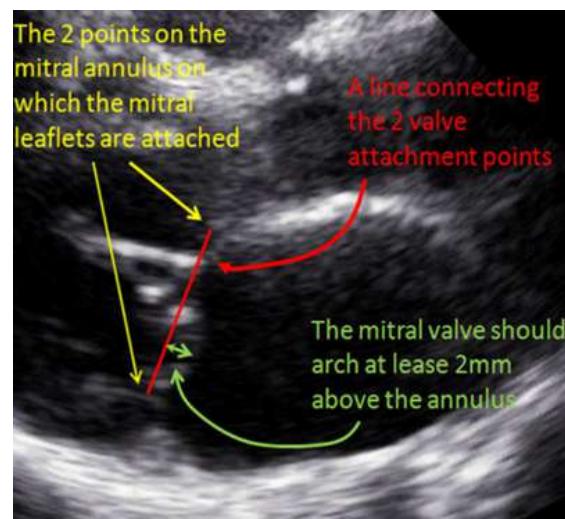


DIAGNOSIS

The most effective method for diagnosing MVP is through **echocardiography**. Two- or three-dimensional echocardiography allows for precise measurements of leaflet thickness and displacement relative to the annulus. Mitral Valve Prolapse is defined as the **displacement of the mitral valve more than 2 mm** above the mitral annulus in a long-axis view, such as the parasternal or apical three-chamber view. The clinical utility of cardiovascular magnetic resonance imaging (CMRI) in diagnosing MVP has not been thoroughly assessed. However, **CMR can accurately quantify mitral regurgitation**, which is valuable information particularly before **mitral valve surgery**. Occasionally, MVP is incidentally detected during left ventriculography performed as part of **cardiac catheterization**. This is characterized by the displacement of mitral valve leaflets into the left atrium along with late systolic mitral valve regurgitation. In such cases, echocardiography should be used for further evaluation of MVP.

[4] **Transesophageal echocardiography (TEE)** is also an important adjunct in selected patients when more detailed visualization of the mitral valve morphology and of the left atrium (eg, to identify **atrial thrombus**) is needed. TEE's significance in assessing MR stems from its close proximity to the left atrium. **When obstacles hinder transthoracic echocardiography**, like annular calcium or a mitral prosthesis causing **acoustic shadowing**, TEE offers a clear perspective.

It offers **improved visualization** of the mitral valve, now even incorporating **three-dimensional (3D) reconstruction** for comprehensive insight into the **underlying pathology**. [6] [7]



TREATMENT

Patients with MVP who are **asymptomatic** typically **don't require treatment** and are managed **conservatively** through **observation** and regular **monitoring**. Those without accompanying mitral regurgitation may be monitored every 3 to 5 years, while those with mitral regurgitation may require annual follow-ups. For MVP patients experiencing symptoms like **chest pain and palpitations**, treatment with **beta-blockers such as propranolol** is recommended.

In cases of MVP with **severe mitral regurgitation**, mitral valve **repair or replacement** may be beneficial. According to ACC/AHA guidelines, mitral valve repair is **preferred before symptoms of congestive heart failure appear**.

Mitral valve repair is preferred over mitral valve replacement, and surgeons usually recommend mitral valve repair instead of replacement, when possible, as it **keeps the existing heart valve** and can help save heart function. Studies have shown **better results in mitral valve repair** for all cause mortality and late mortality. In general, **a good mitral valve repair is better than replacement**, but in case the operator is unfamiliar with this procedure, it is preferable to replace the valve. Symptomatic patients with significant comorbidities that pose a surgical risk may be considered for **transcatheter mitral valve repair**. [9]

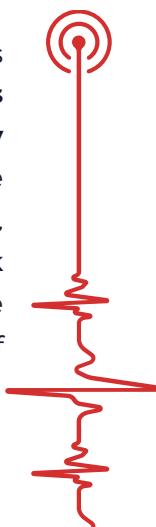
Individuals with MVP are at a **heightened risk of bacterial endocarditis**. While previous guidelines recommended **antibiotic prophylaxis** before invasive procedures, including dental surgery, **newer guidelines suggest reserving prophylaxis** for patients with **other cardiac conditions** at the highest risk of infective endocarditis-related adverse outcomes, as the **risk of antibiotic-associated adverse effects** exceeds the benefit from prophylactic antibiotic therapy for MVP surgical candidates. [8]

The AHA provides recommendations for athletes with MVP. **Athletes engaged in high-intensity competitive sports** may participate based on their **clinical history**, provided they lack certain **risk factors** such as syncope, severe mitral regurgitation, or a history of embolic events.

Athletes can engage in low-intensity competitive sports even with certain risk factors, **under careful consideration**.

PROGNOSIS

The **overall prognosis** for MVP is **benign**. Most asymptomatic individuals are not aware that they have MVP and **do not require treatment**. **Complications** associated with MVP include **infective endocarditis, mitral valve regurgitation, arrhythmia** (atrial fibrillation), **transient ischemic event**, or **systemic embolism**. The estimated incidence of sudden cardiac death in mitral valve prolapse is **217 events per 100 000 person-years from previous studies**. The major predictor of mortality in MVP is **the degree of mitral valve regurgitation and ejection fraction**. Most cases had bileaflet involvement (70%) with redundancy (99%) and nonsevere mitral regurgitation (83%) [10]



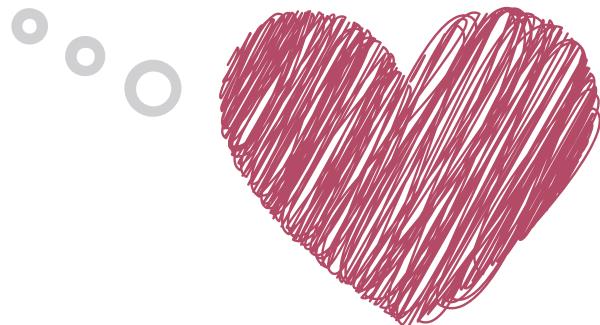
REFERENCES



TAKOTSUBO CARDIOMYOPATHY: Is it as scary as it sounds?

WRITTEN BY NIKOLAOS ZIOGAS
EDITED BY ELENI TZANETOU
DESIGNED BY APHRODITE P. PASCOE

Takotsubo Cardiomyopathy (TC), also known as stress-induced cardiomyopathy, is a condition mimicking acute coronary syndrome (ACS). Although, it was initially thought to affect mainly Japanese population, many cases have been reported worldwide in the last decades. Most commonly, it involves post-menopausal women. However, if men are affected, they show a worse prognosis. The exact pathophysiology behind the disease is not very well established, with the most widely accepted theory involving the over activation of sympathetic nervous system, resulting in hypersecretion of catecholamines and thus causing microvascular spasms and myocardial ischemia. The increase in catecholamine release is triggered by both physical and emotional stressors. Its typical clinical presentation is chest pain accompanied by ECG changes, mildly elevated cardiac enzymes and wall motion abnormalities. Treatment differs based on the severity and acute complications of Takotsubo syndrome. Even though it is considered a benign disease, mortality rate ranges between 0-8%. [1], [2]



DEFINITION

Takotsubo Cardiomyopathy (TC), commonly called broken heart syndrome, is characterized by transient regional systolic dysfunction of the left ventricle without angiographically significant coronary artery disease or acute plaque rupture. First described in Japan in 1990 by Sato and Coworkers, the term Takotsubo is taken from the Japanese word meaning octopus trap, due to the characteristic apical ballooning appearance of the left ventricle. [3]

EPIDEMIOLOGY

Takotsubo syndrome is thought to affect most commonly women after menopause, in more than 90% of cases. The reason behind this is not clear, however the decrease in estrogen levels may play a pathogenic role. Overall, TTS has been reported in approximately 1% to 2% of all 'troponin-positive' suspected ACS presentations and almost 6% of all women presenting with suspected STEMI who undergo urgent angiography. [2]

EDGE OF MEDICINE

PATOPHYSIOLOGY

The exact pathophysiology behind the disease is not very well established. However, the most widely accepted theory involves the overactivation of the sympathetic nervous system, causing an increase in catecholamine levels. Hypersecretion of epinephrine and norepinephrine is triggered by several physical or emotional stressors, such as the death of a loved one, great financial loss, CNS disorders (Stroke, Seizures), malignancy and surgery. The mechanism behind the disease involves the large coronary epicardial arteries and the smaller conduit arteries (coronary pre-arterioles, arterioles and capillaries). More specifically, the vasoconstrictive effects of catecholamines lead to an oxygen supply/demand mismatch, which results in macrovascular and microvascular spasms and ischemia. Furthermore, an impairment in vasodilatory ability of small coronary arteries can also cause microvascular dysfunction and thus ischemia. Both mechanisms result in MINOCA, which is myocardial infarction in the absence of a coronary artery obstruction. So, we can support that TC is included in MINOCA.[4]

CLINICAL PRESENTATION

TC resembles acute MI. It typically appears with chest pain and dyspnea. Some patients also present with signs and symptoms of heart failure, arrhythmias or even with transient ischemic attack.[4]

DIAGNOSIS

Takotsubo Cardiomyopathy is difficult to be diagnosed as it greatly resembles Acute Coronary Syndrome. For this reason, there have been some diagnostic criteria established to make the diagnosis easier. These are the Mayo Clinic Criteria developed in 2004 and InterTak Diagnostic Criteria in 2018. Their main differences are that InterTak diagnostic criteria support the presence of atherosclerosis on coronary arteries, as well as that Pheochromocytoma can be a trigger for Takotsubo.[4]

INVESTIGATIONS

Electrocardiography (ECG) should be done on any patient with chest pain or suspicion of TTS. It usually shows ST- Elevations on Leads V2-V6 and T wave inversion on several leads. The most important finding is that there are no reciprocal changes on leads II, III and aVF (Mirror Image), which is helpful for excluding STEMI. However, the ECG changes are non-specific and non-diagnostic for Takotsubo Syndrome. [4]

Echocardiography is the first imaging tool used in the acute phase of Takotsubo. It typically shows an apical and mid-ventricular wall hypokinesia along with a basal wall hyperkinesia of the Left Ventricle. This wall motion abnormality gives the characteristic appearance of an “apical ballooning”, indicative for diagnosis of TC. [4]

Cardiac biomarkers such as Troponin I, Troponin T and Creatinine kinase (CK) are mildly elevated in comparison with acute MI patients. However, this elevation is not proportional to the bad clinical picture of the patient. In fact, a small proportion of patients do not have elevated cardiac enzymes at all. Thus, even the absence of enzyme elevation does not exclude the diagnosis. [4]

Coronary angiography is the best tool used for diagnosis confirmation. Patients with TC have clear coronary arteries or atherosclerosis but with an obstruction less than 50%. The absence of coronary occlusion

more than 50% excludes Acute Coronary Syndrome. In addition, a left ventriculography showing an apical dyskinesia and a basal segment hyperkinesia are crucial findings for the diagnosis of TC.

[4]

In the acute phase, reversible myocardial inflammation and oedema are hallmark findings of TTS. Edema is transient and usually resolves within 6 months. The absence of late gadolinium enhancement helps exclude the diagnosis of Myocarditis. [4]

MANAGEMENT

In acute phase treatment, the goal is to prevent complications of TC, such as Heart Failure, Cardiogenic shock, Life-threatening arrhythmias and Thrombus embolization. On the other hand, long term management involves the use of Beta blockers and ARBs/ACE inhibitors for at least 3-6 months. Then a serial imaging is required to evaluate the wall motion abnormalities. In fact, the use of ACE inhibitors or ARBs for maintenance showed a lower prevalence of TC recurrence.[4], [5]

PROGNOSIS

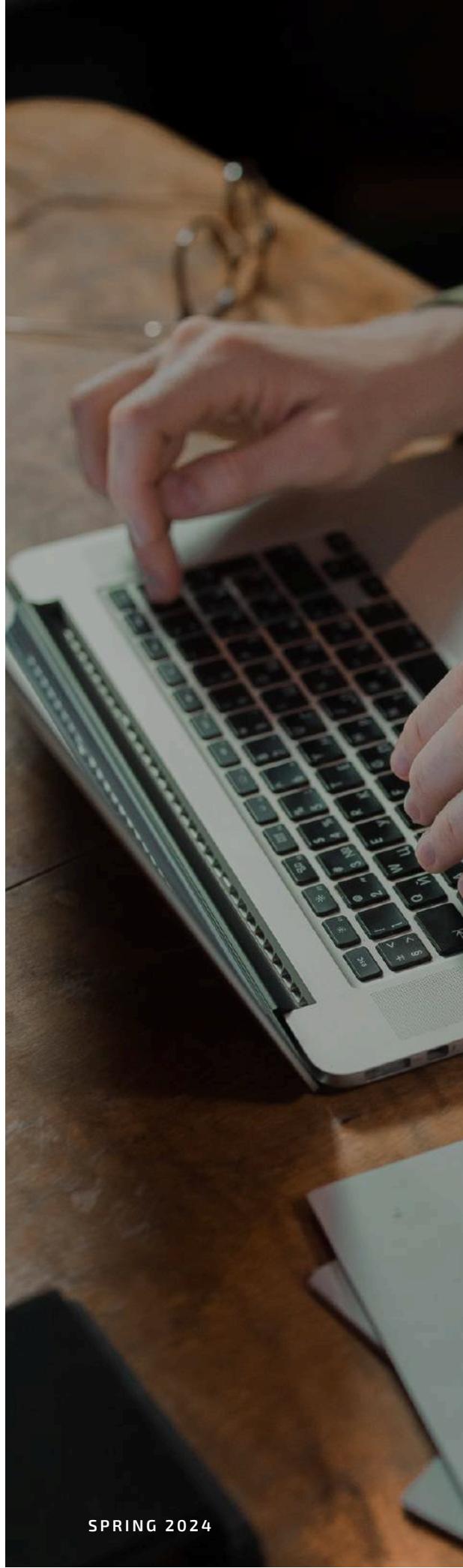
Although TC is considered a benign, transient condition, it has a mortality rate that ranges between 0-8%. Males, even though less affected, they show a worse prognosis. Finally, TC caused by physical stressors is associated with worse in-hospital and long-term outcomes. [4]

CONCLUSION

In Conclusion, Takotsubo syndrome, although it is not as scary as it sounds, it can be life-threatening, if left untreated. It is characterized as a Transient Left Ventricular dysfunction triggered by some physical or emotional factors, causing an overactivity of the sympathetic nervous system and hypersecretion of catecholamine release, thus resulting in myocardial dysfunction and ischemia. On Clinical presentation, it usually mimics Acute Coronary Syndrome. Furthermore, the increased prevalence of TC in post-menopausal women may indicate a correlation with the decreased estrogen levels that are observed on that age group. Finally, concerning Treatment, the main goal in acute phase is to prevent the complications of TC. On the other hand, in stable patients, administration of ACE inhibitors or ARBs along with beta blockers seem to be beneficial in counteracting the pathophysiologic mechanism of the disease.

REFERENCES





WRITERS *JOIN US!*

From breaking news to deep dives into specialist topics, join the writing team to explore and share your scientific interests!

**JOIN EUC MEDICAL
SCHOOLS' FIRST
STUDENT-RUN
MEDICAL JOURNAL.**

[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

The Role of Metabolism on Cancer Pathogenesis:

Why Genetics Is Not the Only Player

WRITTEN BY ROSA TSUCALA
EDITED BY ANNA ANGELAKI
DESIGNED BY APHRODITE P. PASCOE

Cancer is considered a **genetic disease** by the majority of modern scientists. Nevertheless, evidence suggests that **metabolic dysfunction** lies behind **cancer pathogenesis**. This article aims to provide a **clear picture of the mechanisms** behind this disease by evaluating the supporting evidence.

INTRODUCTION

Cancer is a disease caused by the **abnormal proliferation of cells** leading to the formation of a **malignant mass**, called a **tumor**. A tumour can be either **benign or malignant**. The primary characteristic of a malignant tumor compared to a benign one is its **ability to metastasize**. Metastasis is the process during which cells from the primary tumor break-off and travel to other parts of the body, where they proliferate. There are **different types of cancer** depending on the original site of tumor manifestation. For example, breast cancer originates in the breast area, and can metastasize to other organs [1].

It appears that although our understanding of cancer has seemingly improved, **cancer burden is on the rise**.

More specifically, it is estimated that in **2050** the amount of new cancer cases will be **77% higher** than in **2022** [2]. Cancer research should **not only focus on elucidating disease mechanisms**, but also ensure that these findings translate to **improved clinical outcomes**. This article aims to explore cancer pathogenesis and uncover whether the driver of the disease is genetic or metabolic.

Cancer as a Genetic Disorder – The Somatic Mutation Theory

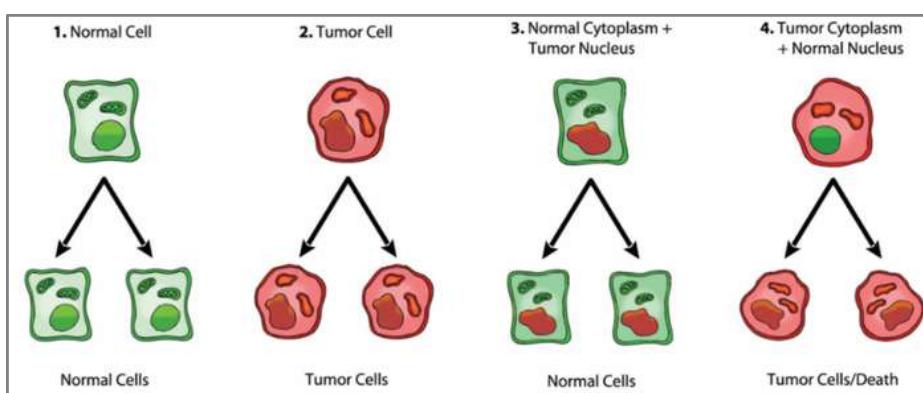
Cancer is commonly perceived by the scientific community as a **genetic disease**. To what extent is this theory true and where did it originate? The **gene theory of cancer** originated in **1914** following **Theodor Boveri's** suggestion that cancer is caused by **abnormal chromosomal segregation** during cell division. Nevertheless, Boveri focused on **developmental cytogenetics** in model organisms and doesn't appear to have directly experimented on cancer.

Although Boveri focused on chromosomal instability behind mutagenesis, his observations were extended to **somatic mutations**, giving rise to the “**somatic mutation theory**” of cancer [3]. This theory is accepted by most modern scientists, although some argue that it should be **reconsidered** [4]. One of the first scientists to question the gene theory of cancer was **C.D. Darlington**. He proposed that cancer arises from **mutations in cytoplasmic elements** which he called “**plasmagenes**” [5].

Are somatic mutations the drivers of cellular tumorigenesis?

Although **cancer cells** do exhibit **mutations**, it is uncertain whether these are the **drivers of the disease** or merely the effect of **uncontrolled proliferation**. In order to investigate further whether nuclear elements are responsible for **tumorigenesis**, **cytoplasmic/nuclear transfer experiments** were conducted [6].

These revealed **inconsistencies** in the somatic mutation theory. More specifically, **Israel et al.** transferred cytoplasm from normal rat epithelial liver cells to tumorigenic cells and showed that **tumorigenicity was suppressed** in four out of five **progeny clones**, as summarized in Figure 1. This indicates that cytoplasmic elements have the ability to **control tumor cell fate**. Moreover, **Mintz et al.** injected five teratocarcinoma cells derived from embryos into blastocysts and subsequently observed their development [7]. They concluded that **carcinogenic cells** exhibit **developmental totipotency** and have the ability to generate **normally functioning adult tissues**. These results, among others, indicate that acquiring tumorigenicity **does not involve changes in genome structure** but rather changes to tissue organization.



[Fig. 1] Summary of nuclear/cytoplasmic transfer experiments indicating that a tumour nucleus combined with normal cytoplasm can give rise to normal cells while a tumour cytoplasm with a normal nucleus can induce tumorigenicity. Figure by Jeffrey Ling and Thomas N. Seyfried [10].

C₃A₁N₁C₃E₁R₁

Evidence that supports the **somatic mutation theory** is mainly based around the concept of “**driver mutations**”. Driver mutations are defined by the National Cancer Institute as “**changes in the DNA sequence of genes that cause cells to become cancer cells and grow and spread in the body**” [8]. Nevertheless, detecting driver mutations is a “notoriously difficult process” as reported by Brown et al. [9]. The **process of detecting these mutations** involves screening large populations of cancer cells for **recurrent mutations** as well as **evaluating their mutability**. Driver mutations have been associated with lower mutability rates compared to passenger mutations (considered to be a result of tumour hyperproliferation and genomic instability).

The limitation introduced by this method is that there is lack of an objective gold standard and criteria to **define a mutation as the driver** [11]. In addition, genomic sequence studies have revealed that there are **over 60 million mutated genes** expressed in different **cancer cells**, thus making the task of developing effective therapies a challenging one [12,13].

Moreover, although **mutations can be common amongst cancer cells**, there is not a single gene mutation that can be found in all cancer cells [12]. This highlights the **increased variation between tumour genomes** and leads us to consider other pathogenic mechanisms.

Overall, although the **somatic mutation theory** is **largely accepted**, it is evident that it presents **inconsistencies**. These urge us to delve deeper behind the notion that cytoplasmic/metabolic elements could be the drivers of cellular tumorigenesis [10].

Cancer as a Metabolic Disease

Otto Warburg was the first scientist to describe **metabolic dysfunction in cancer cells** and was awarded the Nobel prize for Physiology or Medicine in 1931 [14]. He described that cancer cells use **anaerobic glycolysis** to generate energy even in conditions where oxygen was abundant [15]. He also hypothesized that this metabolic pathway is an adaptation of the cell to **insufficient respiration** [16]. The main pathway that is affected during **lactate production** is **oxidative phosphorylation**, which takes place in the mitochondria [17].

This indicates that during cancer pathogenesis **dysfunctional mitochondria** can lead to **impaired respiration** and upregulation of the **glycolytic pathway** [10]. **Anaerobic glycolysis** is sustained through the production of **oncometabolites**: endogenous cellular metabolites that assist in tumor growth and proliferation [18].

These **oncometabolites** can also **act as transcription factors**, altering gene expression and **inducing tumor formation** [19]. The evidence mentioned above dictate that **metabolic dysfunction precedes genetic instability** by being the driver of altered gene expression itself.

CONCLUSION

Having in mind the aforementioned, it can be concluded that there is an **abundance of evidence** supporting that the mechanism of cancer pathogenesis involves **metabolic dysfunction**. This is characterized by **mitochondrial dysfunction** which involves increased **oncometabolite production** and the upregulation of anaerobic glycolysis. Nevertheless, a combination of genetic and metabolic factors contributes to the **growth and metastasis of tumours**. Therefore, future studies must focus on **translating these findings** into **therapeutic approaches** that consider lifestyle choices, which **promote metabolic health**.

REFERENCES



Leptomeningeal

WRITTEN BY ELENI ZOUGANELI
EDITED BY BANO IMTIAZ
DESIGNED BY APHRODITE P. PASCOE

CARCINOMATOSIS

Leptomeningeal carcinomatosis (LC), a rare yet serious complication of cancer, is characterized by the dissemination of malignant cells to the meninges enveloping the brain and the spinal cord. Typically manifesting in advanced stages of malignancy, LC, also known as carcinomatous meningitis or leptomeningeal metastasis, is associated with high morbidity and mortality rates. The diagnostic process of LC poses challenges owing to its diverse spectrum of neurological manifestations, often overlapping with those of other pathological conditions. Treatment modalities primarily focus on palliative care, aiming to alleviate symptoms and optimize neurological function. Despite the availability of various therapeutic strategies, a definite cure remains elusive.

Leptomeningeal carcinomatosis, an infrequent complication of cancer, denotes the dissemination of malignancy from its primary site to the meninges enveloping the brain and spinal cord. Leptomeningeal carcinomatosis (LC), alternatively referred to as "leptomeningeal metastasis" or "carcinomatous meningitis", denotes the infiltration of cancer into the pia mater and arachnoid mater of the brain (the two layers of the leptomeninges), encompassing the intervening subarachnoid space, where in cerebrospinal fluid (a transparent, colorless bodily fluid present in the

tissue enveloping the central nervous system) is housed. Most solid tumors have been identified as potential contributors to leptomeningeal cancer. Among individuals affected with solid tumors, the incidence of leptomeningeal metastases ranges from 5 to 10% per 100 patients. Notably, this complication predominates in cohorts diagnosed with breast or lung cancer, as well as melanoma. Conversely, within the demographic of individuals affected with hematologic malignancies, the prevalence of leptomeningeal metastases extends from 5 to 15% per 100 individuals. Furthermore, leptomeningeal metastasis carries high rates of morbidity and mortality; If left untreated, median survival is 4-6 weeks. If treated, median survival is 2-4 months.

Leptomeningeal carcinomatosis develops as a complication of late-stage cancer. This disorder ensues upon the dissemination of tumor cells into the cerebrospinal fluid (CSF) within the subarachnoid space, which delineates the arachnoid membrane from the pia mater. Tumor cell dissemination may occur through hematogenous or lymphatic pathways, direct extension from a primary intracranial neoplasm, or seeding after surgical resection. The symptoms of carcinomatous meningitis exhibit considerable variation and frequently encompass

a spectrum of neurological problems. Specifically, leptomeningeal metastases typically manifest through the presentation of multiple cranial neuropathies or spinal radiculopathies (Radiculopathy, also known as a "pinched nerve", is the compression of one or more nerves at their spinal roots). Notably, numbness within the distribution of the mental nerve, often referred to as "numb chin syndrome," may serve as a distinctive clinical hallmark. Headache represents a prevalent symptom, with alterations in mental status and seizures observed in advanced stages of the condition. Other symptoms may include lethargy, confusion, nausea, vomiting, hearing and vision loss. Diagnosing leptomeningeal cancer poses challenges due to its symptom overlap with other neurological disorders. More specifically, diagnosis entails a comprehensive assessment, including clinical evaluation, brain and spine imaging via MRI or CT scans, and analysis of cerebrospinal fluid obtained through a lumbar puncture (A lumbar puncture involves inserting a needle into the lower back, specifically between the vertebrae of the spine.). In rare cases, biopsy of the leptomeninges or brain can provide an accurate diagnosis, especially if the primary malignancy is unknown.

The management of leptomeningeal metastases is personalized according to various factors such as histological subtype, prognosis, the extent of central nervous system (CNS) involvement, and systemic disease status. Treatment modalities for individuals diagnosed with leptomeningeal metastasis originating from solid tumors primarily focus on palliative measures. These interventions aim to alleviate pain while enhancing neurological function for as long as possible. Analytically, treatment options encompass a range of modalities including systemic chemotherapy, radiation therapy, targeted agents, intrathecal therapy, and immunotherapy. While innovative treatment modalities can slow down the progression of the disorder, a cure has not yet been found.

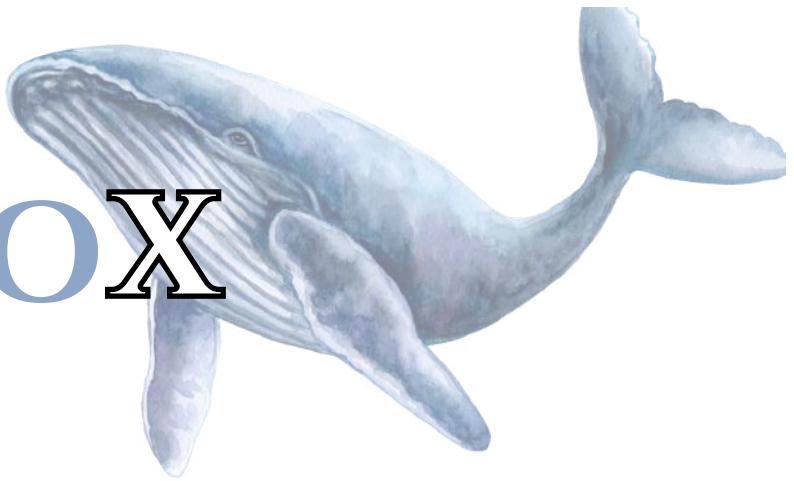
In conclusion, leptomeningeal carcinomatosis represents a challenging complication of cancer, characterized by the dissemination of malignant cells to the meninges enveloping the brain and spinal cord. Despite its infrequency, this condition poses significant challenges, with high rates of morbidity and mortality. Diagnosis is intricate due to symptom overlap with other neurological disorders. While treatment modalities are available, they predominantly focus on palliative measures aimed at alleviating symptoms and enhancing neurological function. However, despite advancements in therapeutic practices, a definitive cure remains elusive.

REFERENCES



PETO'S PARADOX

WRITTEN BY ANASTASIOS VILLIAS
EDITED BY ANNA ANGELAKI
DESIGNED BY APHRODITE P. PASCOE



Cancer's mystery remains a riddle that this article attempts to solve by the ~~extincting~~ puzzle of Peto's Paradox: bigger animals show lower cancer rates per million cells. This article explains some of the biological dimensions of oncology, ranging from oncogenic cellular processes, and mutagenesis to evolutionary invention, to unravel Peto's Paradox. Additionally, the balance of cell cycle regulation and mechanisms of tumor suppression while highlighting the exceptional hypertumors and diverse insights into tumorigenesis created by some life forms. Hence, this article underscores that various life forms hold the key to decoding Peto's Paradox and eventually, defeating cancer.

Cancer, in all its mystery, horror, and perils, has always been one of the most thoroughly researched and widely discussed diseases in science. As scientists strived to understand this daunting enemy and develop effective techniques to counter it, they encountered a strange phenomenon that came to be known as Peto's Paradox.

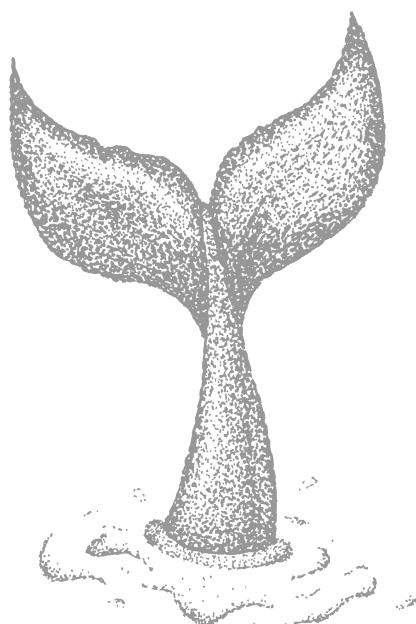
The core observation of Peto's paradox is that, per million cells, bigger animals have a lower probability of cancer. While this phenomenon adds complexity to the issue of cancer for reasons that will be discussed below it also shows that the nature of oncology is much more complicated than it might seem. This phenomenon adds complexity to the issue of cancer and shows that the nature of oncology is much more complicated than it might seem. Understanding the ramifications it requires getting to the bottom of what cancer is and how it occurs.

Human bodies are made up of intricate systems of cellular machinery that are governed by an extensive network of biochemical pathways. These pathways regulate everything from metabolism to DNA replication at the cellular level. However, this extraordinarily complex system is far from perfect. Mistakes in cell division occur constantly, with all but extreme precision, enabling mutations to accumulate over time as errors in regular cells' genetic material.

The body has a method to escape mutant cells - programmed cell death or apoptosis, however sometimes, a mutated cell will avoid apoptosis and lead to carcinogenesis.

The discrepancy in cancer prevalence within species of different sizes is counterintuitive. Primarily, one would dare to assume that larger animals are characterized by more cells and drawn-out lifespans, and, therefore, would grapple with cancer more frequently. However, the empirical data indicates that the situation is quite the opposite. For instance, both humans and mammals can serve as perfect examples of this fallacy. Humans have around 2000 times more cells and exist 50 times longer than mice; however, the rates of cancer seem to be the same. Secondly, the situation becomes even weirder when observing magnificent giants such as a blue whale. Having about 1,000 times more cells than humans, their susceptibility to cancer is exceptionally low, thus making this situation more profound as compared to the first one. Numerous theories have been proposed to explain the reasons behind Peto's Paradox, and we will elaborate on the two most renowned hypotheses.

Approximately 600 million years ago, multicellular beings emerged on the planet, and, gradually, an extraordinary tendency was noticed. Animals began growing and evolving, resulting in the increased size of relatively big beings. Simultaneously, the number of organism's cells rapidly multiplied. Such growth exposed a conundrum for the collective. The peculiar question arose: how to individuate organisms, making them resistant to the proliferation of cancer under circumstances where the number of cells constituting animals' bodies had noticeably gone up. There were two possible solutions: the first implied the development of tumor-preventing measures, while the second was perishing due to uncontrolled cancer growth. Therefore, those beings that were unable to tackle this issue experienced demise due to cancer, while those who developed measures preventing cancer continued their path in the evolutionary process.



Cancer development and progression are predicated on mutations occurring in a class of genes called proto-oncogenes. When a mutation happens, the proto-oncogene becomes an oncogene, which drives cellular behaviors such as increased proliferation, elevated resource consumption, and malignancy phenotypes. For example, early on, a mutation may prevent a cell from committing suicide, the process of apoptosis, allowing the cells to live and proliferate despite genetic damage. Later mutations may assist the cell in evading immune surveillance, acquiring more resources, or behaving in any other ways that help it thrive. These myriad mutations, which acquire traits fuelling proliferation and metastasis, allow the tumor to continue developing.

Tumor suppressor genes function to prevent proto-oncogenes from becoming cancer-causing oncogenes. These guardian genes monitor the properties of their own cells, clone them, and then eliminate any that demonstrate abnormal behavior. They regularly and precisely eliminate cells that are non committing along with any other that show features that have been linked to cancer cells. Therefore, tumor suppressor genes form a frontline against the prevention of cancer cells. However, such a defense against cancer would be unsuccessful if the animal also mimics the triviality of elephant mass.

Alternatively, there exists a balance whereby elephants have enhanced tumor suppression capability. Elephants contain nearly twenty copies of p53, a gene that causes death and repopulates and prevents cells with severe abnormal behavior. Yet, because of this genetic investment, there is no such thing as an inflexible meal. One must give something in exchange to obtain something else. Hence there could be a cost to the trade. In the course of adaptation, this balance leads to faster aging after a certain time threshold or impaired wound regeneration.

An unusual twist to the story of cancer and its novel features across species played a role: the hyper tumours. The name is borrowed from hyperparasites—parasites on parasites, and it gives new insight into the possible dynamics of tumorigenesis and the potential for cancer cells to act as parasites against their own. Cancer in a way is an abrogated long-term cellular pact. In just about any multicellular organism, cells reach to one another and form intricate structures that are crucial for the larger organism's survival. Nonetheless, in the case of tumors, cells betray this pact, and instead of maintaining the status quo by supporting each other, they help themselves to more and more resources. And yet, despite the fact that the benefits of becoming a single tumorous membrane are huge, there is one significant limitation: many cells are needed to form a tumor as they need a lot of nutrients.

If the cells around the primary growth outgrow one, they will compete for the necessary supply of nutrients. To overcome the problem, cancer cells force the vasculature of the host to start sprouting blood vessels from existing ones into the tumor tissue, providing the tumor with all the necessary nutrients to encourage its growth. Nevertheless, there is one unique factor that plays a role in the fate of cancer cells: mutations. In the maze of robust proliferation, random mutations lead to the rapid genetic change of all the cells in the tumor. As a result, some cells begin to vary in their mutation rate. Some of them become known as hypermutants.

The implications of such ongoing cellular rebellion are staggering. Hyperproliferative tumor cells upset the well-developed balance of the tumor microenvironment and initiate a series of events that lead to the demise of a former ally. By resources from the original tumor mass, these newly discovered entities ultimately force the cancer cells into a war for nutrients, resulting in the original tumor's destruction. The potential significance of hyper tumors in the context of Peto's Paradox - the observation that larger animals have a lower incidence of cancer than they should - should not be underestimated. It is possible that numerous hyper tumors are more prevalent in animals of substantial size than currently believed.

Therefore, it is challenging to find a tumor that has grown so large as to be clinically detectable. A 200-year-old blue whale could appear on a biopsy slide as a mosaic of microscopic hyper tumors, all non critically positioned. While these fascinating uses for large animal anti-cancer arsenal are fascinating, they only tell part of the story. Others suggested underlying differences that could be responsible for cancer immunity, such as variations in metabolism or genetic makeup, all must be thoroughly investigated. Scientists are learning everything there is to know about this enigmatic new weapon against cancer by dragging it out from the darkness in which it lurks.





EDITORS *JOIN US!*

Read about a wide variety of scientific topics and help edit articles for greater clarity by joining our editing team!

JOIN EUC MEDICAL SCHOOLS' FIRST STUDENT-RUN MEDICAL JOURNAL.

[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

Influenza Vaccination

during

PREGNANCY:

Is it SAFE?

ABSTRACT

Seasonal influenza vaccination is considered of outmost importance and should be encouraged among the pregnant population. During pregnancy, a woman's immune system struggles to fight off pathogens, which makes her more susceptible to this serious infection known as the flu. Several studies have investigated the effectiveness of such vaccination during pregnancy and have depicted various outstanding and promising effects aiming both at the mother's as well as the fetus's health protection. In addition, The CDC (Center of disease control and prevention) claims that many clinical trials, observational studies, and data from safety reporting systems have consistently shown that such vaccination during pregnancy has an excellent safety profile and could successfully prevent many life-threatening influenza-associated complications.

A very controversial yet negligible topic will forever be the vaccination program among pregnant women.

WRITTEN BY DIMITRA SKARTADOU
EDITED BY ANNA ANGELAKI
DESIGNED BY NOORA ALKETBI

Influenza has been reported to cause many adverse effects to the pregnant population in comparison to the females of reproductive age who are not pregnant, which could potentially lead not only to hospitalization but could also affect the developing fetus's health [1]. In addition, women during gestation period, are more susceptible in developing severe influenza complications due to the changes in their immune system as well as the changes in their pulmonary and cardiovascular compartments. Unpredictable as it, the flu could progress to a more serious clinical profile and pregnant women are at greater risk for serious complications including pneumonia, ear infections, dehydration, sinus infections, as well as worsening of any pre-existing chronic conditions such as asthma, congestive heart failure, or diabetes [2].

Many studies have shown that this type of vaccination during pregnancy has many long-term postpartum beneficiary effects on the newborn since the antibodies are passed on from the mother to the fetus which along with its excellent safety profile offers protection to the newborn until his/her first flu vaccine shot at the age of 6 months old [3]. A 2013 case study according to CDC (Center for Disease Control and Prevention) depicted that during 2010-2011 and 2011-2012 flu seasons, immunization decreased the incidence of flu-associated acute respiratory illness in pregnant women up to 50%. These findings are consistent with the predicted range of flu vaccination efficacy among individuals aged 18 to 64 years. Furthermore, according to a 2018 study, having a flu vaccination minimized a pregnant person's chance of being hospitalized due to influenza by an average of 40% [1]. Infants less than 6 months old are extremely vulnerable to influenza, with hospitalization rates comparable to those of the older population. Given that influenza vaccines are ineffective at this age group, the best evidence-based method is to provide trivalent inactivated vaccines during pregnancy. Immunization with such vaccines through the second and third trimester aim at protecting both the pregnant woman and her newborn as well as decreasing the risk for low birth weight.

Itimately, millions of pregnant women who have received the vaccine against influenza over the last several decades have reported outstanding outcomes regarding the protection from this seasonal infection for both themselves and their developing fetus.

REFERENCES

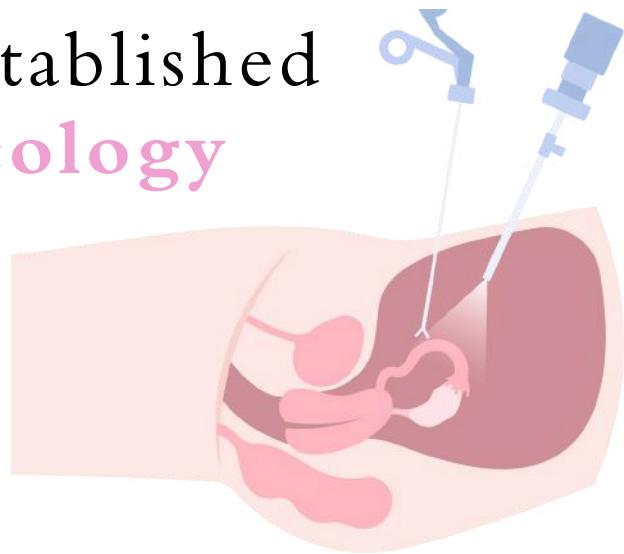


Laparoscopy: an established alternative in gynecology

WRITTEN BY KATERINA TSILAKI
EDITED BY SIMA SALEH-BEY-KINJ
DESIGNED BY APHRODITE P. PASCOE

Laparoscopy is a type of surgery widely used in the gynecology field. This article aims to highlight the numerous advantages it presents, opposed to open surgery, while also informing about possible complications and explaining the procedure and healing process. It is a minimally invasive surgery with fewer complications, shorter hospital stay and very little bleeding. However, side effects like pain, wound bruising and minimal bleeding need to be considered. The procedure includes general anesthesia and the use of a laparoscope as the main tool. The patient should be released after a few hours or days depending on the purpose and the complexity of the procedure. Laparoscopy is an innovative medical procedure that has made many gynecological procedures less troublesome for the patient.

It is no secret to the medical community that the laparoscopic approach to surgeries has gained great popularity over the recent decade. Gynecology is with no doubt one of the specialties benefited the most; Minimum bleeding, faster recovery, fewer post-operation complications and minimal hospital stays.



These are just a few of the numerous advantages opposed to the traditional surgical approach. It is important to mention that though the procedure can be challenging, it may require long hours and special training. Training takes place in certain hospitals and entails both practical and theoretical courses. The laparoscopic approach in gynecology contributes for two purposes, that being: diagnostic and therapeutic. There are a variety of procedures that can be done laparoscopically. These include dealing with endometriosis, ectopic pregnancies, and polycystic ovary syndrome as well as removing fibroids, ovaries and cysts. Laparoscopy is a very useful asset in fighting cancer of the uterus, cervix, ovaries and fallopian tube, as long as the cancer is in its primary stages.



So, what exactly is laparoscopy and how do surgeons proceed towards this method? Laparoscopy is a type of surgery that aims to replace traditional open surgery, that allows the surgeon to have a full view of the internal organs and requires a large incision. The most prominent difference between the two, is that laparoscopic procedure is minimally invasive. A laparoscope is used by the gynecologist to gain access into the pelvis and the abdominal cavity by inserting it through a small incision, made with a scalpel. The cut made is approximately 0.5-1 cm, making the procedure minimally invasive. A laparoscope is the primary tool used in laparoscopy and it is a telescope that resembles a thin, long tube. It has a camera that connects to a video monitor, sending clear imaging of the targeted area and organs to the surgeon. The laparoscope is used alongside a few other tools, in therapeutic laparoscopic surgeries. Such tools include a gas tube used for inflating the pelvis, a needle driver for the suturing of the cut, a bowel grasper to retract tissue and a surgical mesh to reinforce the repaired tissue. Not all of these tools are required for every procedure, their use depends on each case.

Whether laparoscopy is needed for diagnostic or therapeutic purposes the patient should prepare accordingly prior to the procedure. Preparation varies depending on each case. However, some standard steps include not consuming food six hours and water two hours prior to the procedure, as the general

anesthesia used could cause the patient to feel symptoms of nausea. If the patient is on medication they may need to skip some doses, depending on the type of medication. Upon hospital arrival, a nurse will take medical history and a urine sample to ensure the patient is not pregnant or suffering from a condition that could complicate the procedure. Once everything is checked and the patient is prepared, they may be instructed to wear compression stockings to prevent deep vein thrombosis or even take anticoagulant medication if the procedure is scheduled to have a long duration.

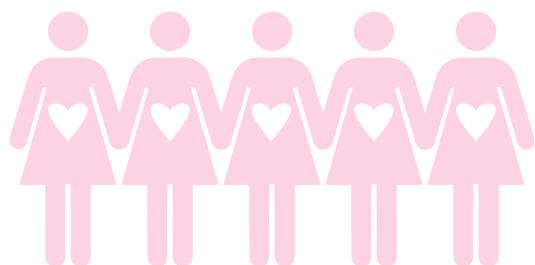
Going through with the actual procedure, the physician will most likely subject the patient to general anesthesia. If the purpose is to diagnose, the duration will be around half an hour to an hour, while if it is for therapeutic purposes, it can take up to several hours. Once the patient is unconscious, the doctor proceeds with making a small cut with a scalpel to insert the gas tube, filling the abdomen and pelvis with carbon dioxide. This causes the abdomen to be inflated, separating the organs from one another away from the internal walls, preventing injuries while providing clear imaging of the area. Moving forward, the doctor utilizes the same cut used initially, to now insert the laparoscope. Once he has visualization on the video monitor, he can continue the procedure. If the purpose is diagnostic the laparoscope may be sufficient as it provides the image, so extra tools are not necessary.

When this is the case, the doctor takes photos and videos, while exerting the laparoscope to summarize the findings of any abnormalities. Lastly, the physician will exit the laparoscope and close up the patient with small stitching.

On the other hand, if the purpose is therapeutic, the gynecologist will need to make one or two additional cuts to insert some more tools depending on the type of surgery. In most cases additional tools are necessary for a cyst, a small organ such as an ovary, or some type of cancer which requires removal. Therefore, a needle and a surgical mesh are also required. After all the tools have been inserted and the doctor has a clear view of the area, he removes the mass or organ, searches the area carefully for more abnormalities, and moves on to release as much carbon dioxide as possible, then when complete, closes and stitches the patient. It is important to note that at any time the gynecologist feels that the view isn't clear, or something is wrong during the procedure, for example, a mass being larger than expected, he has the authority to call for an open surgery. Meaning he can convert to traditional open surgery in order for the procedure to be as beneficial to the patient as possible.

Once the procedure is over and the patient wakes up from the anesthesia, rest is required. As the anesthetic effects reduce, there might be some discomfort or pain, so painkillers will be provided.

Seeing as the patient was under general anesthesia the preferred painkillers are NSAIDS, including ibuprofen, celecoxib and naproxen sodium. The pain is attributed to the gas used to fill up the pelvis and abdomen, more than it is to the actual incision site, as it is very small. If the laparoscopy was diagnostic, hospital stay is usually not necessary and the patient should be able to get back to their normal activities after a couple of days. If it was therapeutic, sometimes an overnight stay is suggested, always depending on the details of the procedure. Also, if the surgery was more complex, full recovery may take up to a few weeks. For both cases, moving the legs as much as possible or wearing compression stockings is advised to prevent blood clots from forming. The patient is also strongly advised to refrain from certain activities like driving for the first 24 hours post-surgery. Vaginal bleeding is expected for the first days and shouldn't be a cause of concern unless it continues for multiple days. When this occurs, the patient needs to alert their gynecologist and with that, the patient will make a follow-up appointment. During the follow-up, the gynecologist will assess the patient's concerns, give advice, and monitor their progress.



Why choose laparoscopy? As already mentioned, it has less complications, faster recovery time, minimum hospital stay, as well as minimum bleeding. It gives the doctor an opportunity to be very precise with mass or cancer removal without potentially removing the entirety of an organ they are operating on; for example an ovary, thus maintaining a woman's fertility. Additionally, the scar is almost non-existent due to the very small incision site, as opposed to the large, non-aesthetically appealing scars that open surgeries usually result in. Moreover, the surgical field has evolved greatly, giving ground for multiple types of procedures to transition to the laparoscopic method in treating cancer, removing masses, ovaries and cysts. Last but not least, women are capable of continuing on with their normal daily life a lot sooner, especially by making a speedy full recovery, as compared to having an open surgery.

Laparoscopy is indeed a great alternative, however it may present a few complications, as well as any medical procedure. Some common unwanted side-effects post-operation include minimal bleeding, abdominal pain, fatigue, wound bruising and feeling of weakness. Furthermore, there are additional long term and more severe complications that a patient could suffer from. Although the incision site might be small, there is a possibility of it being infected, or bulging of skin near the wound site (a condition called hernia).

A urine infection could occur as well, causing discomfort when peeing and polyuria. During the procedure, there is a chance that an organ might have been damaged, resulting in additional pain. Lastly, if the patient does not wear compression stockings, deep vein thrombosis is also a possibility that can cause a very serious condition, especially if it reaches the lungs. All of the above are risks concerning all patients and should be well taken into account when concerning patients that are obese, elderly, suffer from a chronic condition or had additional abdomen procedure, as they are more susceptible to complications.

To conclude, laparoscopy has set a new path for gynecology making some very painful and complicated procedures much more comfortable to the patient. It is a type of surgery that has shaped modern medicine and completely transformed the gynecology field. However, just like every procedure it carries some risks that need to be considered. As a medical student myself, and a person that has undergone laparoscopy, I feel confident to say that it is a procedure developed with a patient centered approach aiming to maximize therapeutic results and minimize unwanted risks and side effects.

REFERENCES





DESIGNERS *JOIN US!*

Enhance your creativity by bringing the authors' and editors' words to life as part of the design team!

JOIN EUC MEDICAL SCHOOLS' FIRST STUDENT-RUN MEDICAL JOURNAL.

[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

Erythema Multiforme Disease and SJS/TEN:

Are they different medical entities?

WRITTEN BY ANNA MAINA
EDITED BY ELENI TZANETOU
DESIGNED BY APHRODITE P. PASCOE

In this **opinion article**, the main goal is to distinguish the similar entities of erythema multiforme and **Steven Johnson Syndrome** (SJS). They have different signs and symptoms. Their **cutaneous manifestations** are differentiated based on the morphology and the clinical progression. Regarding the **etiology**, newly administered drugs and infectious causes predominate. The similarity of **SJS** and **Toxic Epidermal Necrolysis** (TEN) is reported according to **symptomatology**. Concerning the body detachment that follows, these two entities are easily distinguished. The conclusion focuses on the importance of **why they should be managed independently**.

There is a **basic categorization** for **erythema multiforme**, this acute immune-mediated condition. Specialists divided it into **erythema multiforme minor** and **erythema multiforme major**. For many years, erythema multiforme major had been **interchangeably used** with the medical terms of **Steven-Johnson Syndrome** and **Toxic Epidermal Necrolysis (SJS/TEN)**. However, in 1993 and 1994, **Bastuji an Roujeau** discussed for the first time the **urgency to differentiate these two entities**. The reasonable question of why this is important arises.

The **main principles** that support the need to **distinguish** erythema multiforme from SJS/TEN **are reported below**. (Hidajat & Loi, 2014)

CLINICAL APPEARANCE

First, it must be clarified that **erythema multiforme** is present clinically in a separate way than SJS/TEN. Erythema multiforme major is **characterized by typical targetoid lesions** with severe **mucosal involvement** in systemic symptoms. (Figure 1.) The **cutaneous manifestations** have a defined border either three or more mucosal sites are involved. It is important to note the **symmetrical distribution of the rashes** that predominate in the extensor surfaces of the body, the neck or the face. The **soles and the flexor compartments are usually spared**.



[Fig. 1] Typical targetoid lesions

In contrast, **atypical targetoid lesions** with a **poorly defined** but **raised border** are encountered in patients with **erythema minor** accompanied with **minimal or even absent mucosal involvement**. (Figure 2.) The main difference between the erythema major and minor is that the **latter one has no systemic symptoms** in clinical history. The clinical appearance of **Steven Johnson syndrome** is described as a **widespread distribution of blisters** in the **face** and in the **trunk**.

They are **macular** and **pruritic**. **Denudation** is a alarmed sign that should make junior doctors suspicious for the presence of **SJS**. In other words, the disease is characterized by the **peeling of the skin**, leaving behind an **erythematous raw red base**. This sign is called **Nikolsky**. (Figure 3.) It is **always positive in SJS, unlikely to erythema multiforme**. Systemic symptoms are worse in SJS. (Jose A Plaza, 2021)



[Fig. 2] Atypical raised lesions

CAUSATIVE AGENTS

The causative agents **differentiate these two medical entities**, supporting the belief that they should be managed independently. They are **provoked** by an extended list of **etiological factors**. Most of the reported causes are being shared in both diseases. However, the **prevalence differs**. **Infectious agents** are mostly responsible in the majority for erythema multiforme in comparison to Steven Johnson syndrome which is mostly **evoked by drugs**. Since SJS is an immune-mediated hypersensitivity disorder, **toxic byproducts** from the **drug metabolism** are involved in the **etiopathogenesis** of the disease. For instance, **non-steroidal anti-inflammatory drugs** are commonly encountered as causative agents of the SJS whereas **antibiotics** such as **sulfonamides** generate, secondary to infections, are believed to cause erythema multiforme. As mentioned above, erythema multiforme is caused by **herpes simplex virus infections**. Most of the patients can present with a prodrome of **influenza-like symptoms** apart from the recurrent ulcers in the oral cavity in the case of herpes simplex virus infection.

Gastrointestinal symptoms and **respiratory** are commonly encountered some days before the first oral manifestation. Mycoplasma pneumoniae agent contributes to the etiopathogenesis of the disease that attacks the children. (Fazel, 2019) **Prognosis is worse** in the case of SJS/TEN. In more details, **mortality risk** for TEN is 30-40 percent with a 5-year survival rate of 65% after the acute phase. (Fazel, 2019) (Feather et al., 2021)

Regarding the **difference between SJS and TEN**, they appear **similarly** in **clinical base**. They differentiated according to the **detachment** of the total **body surface**. Besides the **shared symptomatology**, SJS has **less than 10 percent of total body surface** detachment compared to TEN where **more than 30 percent of epidermal necrolysis** follows. An overlapping syndrome has an intermediate range between 10-30% of epidermal detachment. (Jose A Plaza, 2021) (Fazel, 2019) (Feather et al., 2021)



[Fig. 3] Nikolsky sign

CONCLUSION

The key message of this article is addressed to **junior doctors**. Differentiating these two diseases as independent entities is **not only for enhancing the literature**. Management of severe life-threatening conditions like SJS/TEN should be the **initial goal**. The presenting complaints of the diseases look **very similar**, but their **clinical course** requires a **different and urgent resuscitation plan**. A patient with Steven Johnson Syndrome has a toxic appearance with constitutional symptoms like fatigue, malaise or fever. In conclusion, erythema multiforme is a self-limiting disease that is being treated to speed up its remission. However, SJS/TEN needs urgent hospitalization and follow up. (Fazel, 2019) (Feather et al., 2021)

REFERENCES



A Review on Herpes Zoster; causes, complications and prevention strategies

WRITTEN BY CHRISTINA MASTORI KOURMPANI & MAGDALINI RIGINA FRANGOULI
EDITED BY JACALINE SKOUROS
DESIGNED BY GABRIELLA KAVVADIA

Herpes Zoster (HZ), resulting from the reactivation of Varicella-zoster virus (VZV), presents a variable clinical spectrum and can lead to severe complications, particularly in immunocompromised individuals. This article provides an overview of HZ pathophysiology, clinical manifestations, treatment modalities, and prevention strategies, with a focus on recent updates post-COVID-19 pandemic. VZV primarily causes Varicella, transmitted via respiratory droplets or vesicular lesion smears. Following primary infection, VZV remains latent in nerve tissue, reactivating later in life to cause HZ characterized by dermatomal vesicular eruptions and intense pain. Unlike Varicella, HZ poses no risk to the developing fetus due to maternal antibodies. Approximately one-third of individuals develop HZ in their lifetime, with increasing age being a significant risk factor. Other risk factors include immunocompromised states and certain medical conditions. Clinical presentation typically progresses through pre-eruptive, acute eruptive, and chronic phases, often requiring clinical diagnosis, though Polymerase Chain Reaction (PCR) aids in atypical cases.

Special clinical patterns, including HZ Ophthalmicus, Ramsay-Hunt syndrome, and Central Nervous System HZ, necessitate thorough examination to prevent complications. Postherpetic neuralgia, meningitis retention syndrome, and vasculitis are potential complications. Notably, HZ may manifest post-COVID-19 infection or vaccination. Therefore, understanding HZ pathogenesis, clinical features, and management strategies is crucial for healthcare professionals, especially in the context of evolving infectious disease landscapes. Herpes zoster, though often self-resolving, presents various treatment avenues, including NSAIDs and antiviral medications like ACV. Advanced cases may necessitate famciclovir or surgery. Recent medications like Valganciclovir and HPIs offer hope. Vaccination, particularly with Shingrix, is vital, endorsed by the CDC, especially for older adults, demonstrating high efficacy.

INTRODUCTION

Herpes Zoster (HZ) represents the reactivation of Varicella-zoster virus (VZV) or human herpes virus 3. Herpes zoster is characterized by variable clinical presentation and can have life-threatening complications especially when it affects immunocompromised patients and patients with comorbidities. The literature is ever-evolving and treatment as well as prevention options are of clinical importance. Following the COVID-19 Pandemic the reactivation of VZV has been a topic of discussion in the scientific community, especially following vaccination. Therefore, this article will focus on the pathophysiology of HZ as well as on the current updates concerning the clinical manifestations, treatment and prevention strategies. [1]

PATOPHYSIOLOGY

The Varicella-zoster Virus (VZV) is responsible for primary infection in Varicella which represents one of the most contagious human disorders and it is transmitted via contact with respiratory droplets or smears from vesicular lesions. Viral replication first takes place in the respiratory tract which is followed by lymph node invasion, viremia and eventually formation of cutaneous vesicular eruptions. Following primary infection VZV remains latent in nerve tissue including dorsal root ganglia, cranial nerve ganglia and autonomic ganglia of the enteric nervous system. [1]

Upon reactivation VZV replicates within the bodies of neurons which is followed by shedding along the nerve to the correlating dermatome. Inflammation and vesiculation is caused which ultimately results in intense pain experienced by the patient. [1]

An important note is that even though Varicella infection in pregnancy can spread to the fetus trans-placentally and result in life-threatening diseases, Herpes Zoster poses no risk to the developing fetus due to maternal antibodies which are transmitted diaplacentally. [1]

EPIDEMIOLOGY

According to the Centers for Disease Control and Prevention (CDC) roughly 1 in 3 people will develop Herpes Zoster during their life and commonly more than once, since herpes zoster follows a recurring pattern.

The risk of developing HZ increases proportionally with increasing age. Most commonly, it affects individuals over 50 years of age and it is hypothesized that this reactivation that is observed is due to the decrease in VZV-specific cell-mediated immunity. Other risk factors include:

- Immunocompromised patients with solid organ or bone marrow transplants, hematological malignancies and solid organ malignancies
- Human Immunodeficiency Virus (HIV) patients
- Autoimmune diseases and immunosuppressive medications such as steroids

EDGE OF MEDICINE

Notably, women have an increased risk of HZ in comparison to men, and Caucasians are more likely to have HZ, however these findings remain unexplained. [2]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Characteristically, Herpes Zoster appears in three clinical stages: a. Pre-eruptive Stage b. Acute eruptive Phase and c. Chronic Phase.

The pre-eruptive phase is characterized by pain or burning in the affected dermatome at least 2 days prior to cutaneous eruptions. Prodromal symptoms can also include headaches, photophobia and malaise. The acute eruptive phase is characterized by the development of cutaneous vesicles which are often multiple, umbilicated and painful. Pain is often severe and usually cannot be contained by corticosteroids. The phase lasts for about 2-4 weeks with the vesicles bursting, ulcerating and drying out. This represents the most contagious stage of HZ. If severe pain persists for longer than 4 weeks, then this is characterized as Chronic HZ. Symptomatology includes dysesthesias, paresthesias, and shock-like sensations. The pain can unfortunately last for several months. Herpes Zoster has a variable clinical presentation and atypical cases are common therefore in most patients' diagnosis is made clinically. Confirmation of suspected HZ-type pain without a rash can be achieved via Polymerase Chain Reaction (PCR). [3]

SPECIAL CLINICAL PATTERNS

As mentioned above, there are many cases of atypical Herpes Zoster. These special clinical patterns include:

1. HZ Ophthalmicus (HZO) in which the ophthalmic division (V1) of the trigeminal nerve (V) is involved. On clinical examination, the majority of the patients present with conjunctivitis, episcleritis, keratitis or retinitis. HZO represents an ophthalmologic emergency as it can lead to vision loss especially in patients > 50 years of age and immunosuppressed patients.
2. Ramsay-Hunt syndrome in which the geniculate ganglion and the facial nerve (VII) are involved. Typical symptomatology involves unilateral facial palsy, otalgia and characteristic painful vesicles on the external auditory canal. The cranial nerves V, VIII, IX and X are also commonly involved.
3. Central Nervous System HZ which affects the CNS and is primarily seen in AIDS/ HIV patients.

The main key point is that a thorough clinical examination is needed in order to exclude any possible special clinical patterns of HZ and of course any future complications.

Complications of HZ can include postherpetic neuralgia, meningitis retention syndrome, erythema multiforme, and vasculitis.

Last but not least, it is important to note that HZ may be a cutaneous manifestation in infection with COVID-19 or following vaccination for COVID-19 with any of the available vaccines. [3]

TREATMENT

In most cases, herpes zoster episodes resolve on their own without treatment and are typically milder in children than in adults. However, there are some treatments that can help alleviate symptoms, potentially reducing their severity and duration, as well as lowering the risk of long-term complications such as postherpetic neuralgia. The choice of therapy typically relies on the individual's immune system status and the specific presentation of the zoster infection. Conservative treatment options for herpes zoster include nonsteroidal anti-inflammatory drugs (NSAIDs), wet dressings with Burow solution, and lotions like Calamine. It is important to mention that uncomplicated cases do not require hospitalization, but severe symptoms, immunosuppression, atypical presentations, or specific complications may warrant admission. [4]



When advanced treatment is needed, the Herpes virus is typically treated with the drug Acyclovir (ACV) and its prodrug named Valacyclovir or Brivudine. These are processed to nucleoside analogues and target the affected cells, blocking the viral DNA replication and consequently shortening the duration and severity of the virus. There are some contraindications related to the renal toxicity, as all those drugs except Brivudine are nephrotoxic. Although an absolute contraindication for Brivudine is the use of fluoropyrimide compounds within the last 4 weeks. The oral form of Valacyclovir has an advantage of a three to fivefold increase in acyclovir bioavailability. While in case of resistance in the ACV caused by mutations in the viral thymidine kinase and/or DNA polymerase, famciclovir is an alternative. [5]

Medications such as steroids, analgesics, anticonvulsants, and antiviral agents are commonly used while surgical intervention is rarely necessary except for certain complications such as Rhizotomy in cases of extreme, intractable pain. [4]

Recently, some other drugs have been proven beneficial against VZV: Valganciclovir, an orally administrable ester prodrug of ganciclovir and Helicase-primase inhibitors (HPIs) such as Amenamevir, which has already been approved in Japan. In immunosuppressive patients the prevention of VZV is of great importance, and a recent retrospective trial among 45 US transplant centers, with a dose of

2 × 400 mg ACV/d most commonly used, showed that low-dose famciclovir is effective as well. [4]

PREVENTION- VACCINATION

It has been suggested that the onset of zoster occurs when the levels of varicella antibody titers and varicella-specific cellular immunity decrease to a point where they are no longer fully effective in preventing viral invasion, making vaccination important.

Since 1995, the live attenuated VZV vaccine has been effective in protecting children and led to a significant decrease in varicella infection and lower herpes zoster rates. However, the impact of childhood vaccination on the occurrence of herpes zoster in adult populations is still not entirely understood, while prevention in older individuals is crucial due to higher zoster frequency and complications. Additionally, the decline in cell-mediated immunity in older age groups increases the risk of zoster. [4]

Currently, Herpes zoster (HZ) vaccines, including the newer higher –potency live attenuated (**Zostavax**; Merck, Kenilworth, NJ, USA) and recombinant adjuvanted (**Shingrix**, GlaxoSmithKline, London, UK) types, aim to prevent HZ and its complications like postherpetic neuralgia (PHN). Studies confirm the safety and efficacy of both vaccines across different patient groups, with the recombinant vaccine showing superior effectiveness and safety for

those with weakened immune systems as it is a non-replicating vaccine. [5]

Zostavax, introduced in 2006, reduced the incidence by 61.1% and the incidence of PHN by 66.5% in adults aged 60 and older and subsequently, the CDC recommended the vaccine for non-immunocompromised, nonpregnant individuals aged 60 and above, even if they previously had zoster. Later, in 2011, the FDA approved its use in individuals aged 50-59, supported by the Zostavax Efficacy and Safety Trial (ZEST), which demonstrated a 70% risk reduction of developing zoster in this age group. The live attenuated VZV vaccine has been effective in reducing both herpes zoster and postherpetic neuralgia, even in individuals with immune-mediated inflammatory diseases. [4]

In October 2017, the FDA approved **Shingrix**, a non-live adjuvanted recombinant zoster vaccine, for adults aged 50 and older. Clinical trials showed over 90% efficacy against shingles across all age groups and sustained efficacy over a 4-year follow-up period. [4]

In fact, trials underscore the considerable benefits of recombinant HZV vaccination in preventing HZ and its associated burdens, particularly among older populations: The NCT02581410 trial examined the impact of recombinant HZV in elderly patients, showing it induced a robust immune response lasting beyond 12 months after the second dose, regardless of prior vaccination status.

In China, a study highlighted the significant public health benefits of mass recombinant HZV vaccination, estimating a substantial reduction in HZ cases, PHN cases, hospitalizations, and outpatient visits, particularly among individuals aged 50-59. Meanwhile, a US claims-based trial demonstrated high effectiveness of the recombinant vaccine in reducing HZ incidence, with an effectiveness rate of 85.5%. Additional US cohort studies further supported the effectiveness of the recombinant vaccine, especially with two doses, showing a significant reduction in HZ cases and related complications, though a rare adverse event of myelin oligodendrocyte glycoprotein-related optic neuritis was noted post-vaccination. [5]

In February 2018, the Centers for Disease Control and Prevention (CDC) approved the 2018 adult immunization schedules, emphasizing the importance of vaccination.

- Administer two doses of recombinant zoster vaccine (RZV) (Shingrix) 2-6 months apart to adults aged 50 years or older regardless of past episodes of herpes zoster or receipt of zoster vaccine live (ZVL) (Zostavax)
- Administer two doses of RZV 2-6 months apart to adults who previously received ZVL at least 2 months after ZVL
- For adults aged 60 years or older, administer either RZV or ZVL (RZV is preferred)

The two vaccines, Zostavax and Shingrix, differ in efficacy and durability of response. Shingrix is recommended for immunocompetent adults aged 50 and older, including those previously vaccinated with Zostavax. Additionally, vaccination with Shingrix has been found to be highly cost-effective compared to revaccination with Zostavax in adults aged 60 and older. Other preventive measures for initial infection include isolating infected patients until lesions crust over and postexposure prophylaxis with VZIG in select populations. [4]

VARICELLA-ZOSTER IMMUNE GLOBULIN

The varicella-zoster virus vaccine is used for prevention, while the CDC recommends administration of varicella-zoster immune globulin (VZIG) can prevent or modify illness in susceptible individuals exposed to the virus. It is advisable to prioritize the use of VZIG for patients who are susceptible to severe disease and complications, including neonates, immunocompromised individuals, and pregnant women. VZIG is most effective when given promptly after potential exposure, although it can still provide benefits if administered up to 96 hours afterward and its protective effect typically lasts for about 3 weeks. [4]

REFERENCES





SOCIAL MEDIA OFFICERS

JOIN US!

Design social media posts and help increase ScienceMind's reach as part of the Social Media team!

**JOIN EUC MEDICAL
SCHOOLS' FIRST
STUDENT-RUN
MEDICAL JOURNAL.**

[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

TREATING BRAIN TUMOURS WITH STEREOTACTIC RADIOSURGERY

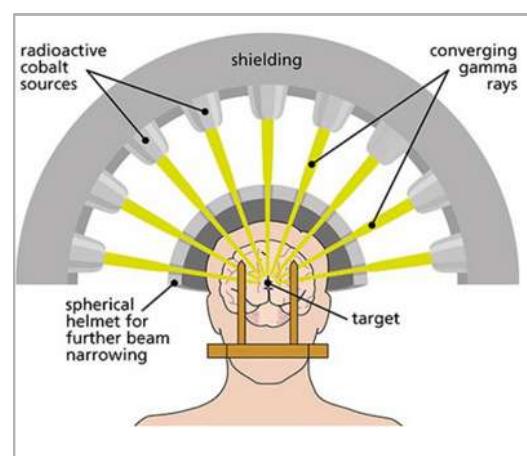
WRITTEN BY ALYSSA HADJIKAKOU
EDITED BY ANNA ANGELAKI
DESIGNED BY APHRODITE P. PASCOE

This article discusses the two principal examples of stereotactic radiosurgery for treating brain tumours: **Gamma Knife (GK)** and **Linear Accelerator (LINAC)**. Both technologies are discussed in terms of their **mechanics, level of precision, and cost effectiveness**. Recent comparative studies have revealed that GK delivers **exceptional precision**, making it **ideal for treating smaller targets**, whereas LINAC was shown to provide increasingly **versatile treatment** options for **larger targets**, and is generally **more cost-effective**. Furthermore, the article emphasises the importance of selecting the **optimal stereotactic radiosurgery method** based on the patient's health, tumour characteristics, and resource availability, to ensure safety and optimise therapeutic outcomes.

Stereotactic radiosurgery is a non-invasive form of **therapeutic radiation**, which uses a **three-dimensional coordination system** to locate specific areas of interest within the body, particularly the brain, and utilises **multiple external beams to destroy target tissue**; two of the most popular forms are **Gamma Knife** and **Linear Acceleration stereotactic radiosurgery** [1][2][3]



Gamma Knife (GK) is a **non-surgical therapy** using **gamma rays** converging on a single point to treat **brain disorders**, such as **tumours**, with high precision to ensure a **maximum dose** while limiting collateral dose to healthy surrounding tissues.[4] The **ionising radiation used is Gamma rays** emitted from the radioactive isotope **Cobalt-60**; which destroys target cells via **DNA damage**. The cobalt-60 sources are arranged into 8 movable sectors inside the unit which surround the patient. **tungsten and lead shielding** prevent unwanted radiation transmission. Fixed channels known as **collimators** create **192 narrow beams of radiation** which precisely focus to intersect at the **isocenter**, which is **positioned exactly in the clinical target** e.g. a tumour.

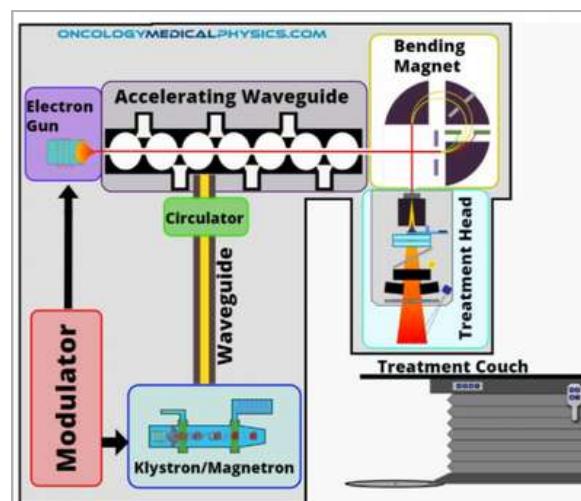


The **beam size** can be altered by moving the **cobalt sources** to one of the **collimator positions**, creating beams of **4mm, 8mm, or 16mm** in diameter. To **prevent head movement** during surgery, a **helmet** is placed on the patient to ensure that the **beams accurately hit the target**.[7] The wearing of the helmet should be the **only source of discomfort** during the procedure. However, if a patient does move, a real-time **infrared motion detection system** tracks movement by using markers on the patient's nose and **automatically pauses the treatment**. An integrated **low-dose CT** imaging system verifies the **patient's position**, and the treatment plan automatically adapts to the target position by **colour registration** of pre-treatment CT images.

Computer software both creates and evaluates the **dose plan**, allowing **delivery adaptation** if needed to ensure that the planned dose is applied as intended. When the treatment is complete, cobalt sources move to the closed collimator position - **stopping the beam**, the patient is automatically moved from the treatment position, and the shielding doors are closed. Patients can usually be in and out of the hospital **within one day**, and back to normal routines within 1 to 2 days after treatment. [5][6]

Another method of stereotactic radiosurgery of brain tumours is **linear acceleration (LINAC)**, which kills or **severely damages tumour cells** via **photon x-rays** through accelerating electrons with **radiofrequency waves**.[8]

Mechanically, either the **Klystron** or the **Magnetron** produce **radiofrequency waves** which are injected into the **accelerating waveguide** alongside electrons produced by the **electron gun**, once combined, the electrons are accelerated towards the **tungsten target**. The electron gun works by heating the tungsten filament within the **cathode** to between $800^{\circ}\text{C} - 1100^{\circ}\text{C}$, with the number of **electrons released** depending on the heating degree. Also, the **accelerating waveguide** contains **copper cells** with small holes in between them to **guide the electrons and focus the beam**. Internally, a **vacuum** is created to ensure the beam is not impeded by other particles, while two sets of **steering coils** and two sets of focusing coils which surround the structure further control the beam. **Electrons then exit** the accelerating waveguide and enter the **flight tube**, where there are **three pairs of magnets** alongside the tube, causing the **electron beam to bend** along the path of the tube to either 90° , 112.5° , or 270° depending on the manufacturer;



this **positions the beam** to strike the target **precisely**, and focuses the beam to a diameter of 1mm. Next, the **electrons hit the tungsten** target where the electron energy is **converted into x-rays**; which are shaped into a precise beam by **primary collimators** and a flattening filter, ensuring **uniformity** and **limiting excess dosage**. The photons then pass through the **ion chamber** for beam quality and dosage management: the **primary decimeter measures the radiation** and terminates the beam when the **required dose** has been delivered, and the **secondary ion chamber** acts as a **backup** in cases of primary decimeter failure. The beam quality function is monitored by a **third ionisation chamber**, which uses **7 electrodes** to monitor different sections of the **radiation field**. Further beam shaping is required to guarantee that the shape of the delivered X-ray beam is identical to the shape of the tumour, this is done with a **multi-leaf collimator** made of fine tungsten leaves.[9][10]

Both the Gamma Knife and LINAC are **highly regarded** stereotactic radiosurgery options for patients seeking treatment for **brain tumours**, however, **which of the two is the superior option** is still up for **debate**. A 2010 Austrian Institute for Health Technology Assessment (AIHTA) study comparing LINAC and Gamma Knife, found **GK to offer superior precision for small targets** like trigeminal neuralgia, while **LINAC provided better treatment homogeneity for larger targets**.

Another point of comparison was **annual cost**: the Gamma knife was found to have an **annual cost of 4,000.000 euros** with an average **lifespan of approximately 20 years**, although, gamma sources need replacing every 5-7 years, costing 700.000 euros each time. Whereas, LINAC had an **annual cost of 3,000.000 euros** with an **average lifespan of 10 years** but was found to need **higher maintenance**.[11] In regards to machine availability, the Gamma Knife is **strictly used for radiosurgery**, whereas LINAC is often **used for conventional radiation therapy alongside radiosurgery**. [12] Nevertheless, internally conducted reports found that the study overall **lacked high-level evidence** from studies that directly compared the two procedures, and stated that no definite conclusions can be drawn. [11]

Recently, a 2020 study published by Radiotherapy and Oncology compared patients with **greater than 2 brain lesions treated with LINAC** to those treated with Gamma Knife; 391 patients with a total of 2699 lesions (LINAC: 1,014, Gamma Knife: 1,685) were identified among two institutions (Ohio State University and Wake Forest), and compared in their survival and radionecrosis differences with Kaplan Meier graphs. Results illustrated **overall similar survival rates between the two procedures** ($HR = 0.86$; 95% CI 0.59–1.24; $p = 0.41$) but stated that Gamma Knife patients were 3.83 times more likely to develop radionecrosis ($HR = 3.83$; 95% CI 1.66–8.84; $p = 0.002$).

medically defined as the **death of healthy tissue because of radiation exposure**.^[13] A second propensity score compared radionecrosis in those treated with Gamma Knife to those treated with single fraction LINAC, suggesting an even **higher incidence with Gamma Knife** (HR = 4.42; 95% CI 1.28–15.29; p = 0.019).^[14] [15]

Nonetheless, physicist Ian Paddick critiqued Radiotherapy and Oncology's study, claiming that although **bias** and **confounding** were factored in, bias is still probable as **patients were treated in completely different hospitals**; meaning an entirely different set of patient care protocols. Paddick continues by pointing out the difference in **patient demographic** and **health status**, with **patients treated with GK being older**, more likely to be **men**, having **greater numbers of lesions**, lower performance status and a **higher likelihood of having concurrent cytotoxic chemotherapy**; despite that, he states that the propensity score matched analysis could potentially override these issues as long as the cohort populations were large enough. In addition, there was no information regarding the amount of previous Gamma Knife treatments undergone by patients undergoing GK in the study. Moreover, Paddick highlights **differences between dosages**; LINAC treatments consisted of 18–24 Gy in a single fraction, 21–27 Gy in 3 fractions, or 25–30 Gy in 5 fractions, with the one selected being based on target size. Furthermore **Biological Effective Dose (BED)** was used to compare single fraction and fractionated

treatments, **LINAC was shown to have lower BEDs**, which is synonymous with **lower rates of radionecrosis**, yet, Paddick argues that single fraction treatments would be predominantly done for **small and safe targets**; potentially creating **bias**. Lastly, in regards to radionecrosis, there were **7 cases (1.3%) of radionecrosis for LINAC** and 26 (4.6%) for Gamma Knife, with the degree of radionecrosis being graded between 1–4, with 4 being the most severe. Paddick states that if **only serious cases of radionecrosis were included**, classified as grade ≥3, the incidences would drop to 0.9% in LINAC and 1.4% in GK; which is **statistically not significant**.^[15]

In conclusion, **both LINAC and Gamma Knife are state of the art** pieces of equipment which present an **array of benefits and drawbacks** that cater to various clinical needs. **LINAC offers flexibility** in its fractionation schemes and is capable of treating higher volume targets, **making it ideal for larger tumours**. Conversely, **Gamma Knife provides extreme precision** in its high dose single fraction treatments, **making it preferred for smaller tumours**. Definitively, which of the two treatments is employed should be decided on a **case by case basis**, taking into account factors such as patient condition and costs, but, above all else, patient safety.

REFERENCES





WRITERS

EDITORS

DESIGNERS

**LAUNCH
YOUR
FUTURE,
with every
edition!**

***JOIN OUR
TEAM!***

This is where curiosity meets science, join our team today and write the next chapter of medical innovation!

**JOIN EUC MEDICAL
SCHOOLS' FIRST
STUDENT-RUN
MEDICAL JOURNAL.**

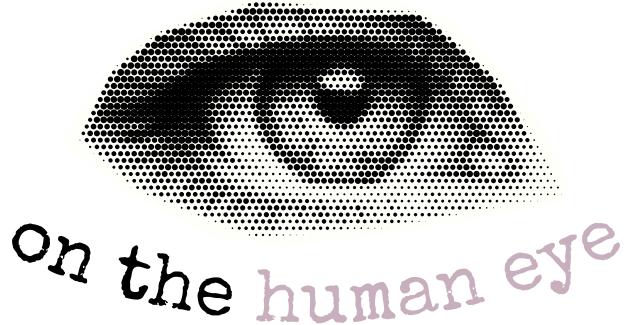
[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

Effects of UV rays

WRITTEN BY CHARILAOS SPANOUDIS
EDITED BY CHRISTOS-RAFAIL KARATHANASIS
DESIGNED BY APHRODITE P. PASCOE

Exposure to **ultraviolet (UV)** radiation from the sun poses significant **risks** beyond skin damage, **extending to the eyes** and **vision**. In this article we explore the **impact of UV rays on ocular health**, emphasizing the importance of **eye protection**. **UV radiation**, categorized into **UVA** and **UVB**, can penetrate the atmosphere, **affecting the cornea, lens, retina, and uvea**. Chronic exposure can lead to conditions such as **photokeratitis, pterygium, macular degeneration, cataracts, and uveal melanoma**, a potentially **lethal eye cancer**. Mitigating these risks requires understanding UV sources, geographic and altitude factors, and protective measures like **UV400-rated sunglasses**, hats, and sunscreen. This comprehensive overview underscores the **necessity of safeguarding vision against UV radiation** for lifelong ocular health.

We all know that we need to **protect ourselves** from the harmful rays of the **sun**, more specifically the **ultraviolet or UV rays** that can cause **skin cancer** among other skin diseases. This is the reason why need to wear **sunscreen** every day when we go outside, especially in the summer. But what if I told you, that your skin is not the only organ in your body that is affected by the UV rays and therefore needs protection. In this article I will briefly go over the ways UV rays can



affect our eyesight, the **potential dangers of exposure** and what you can do to **safeguard your vision** for years to come.

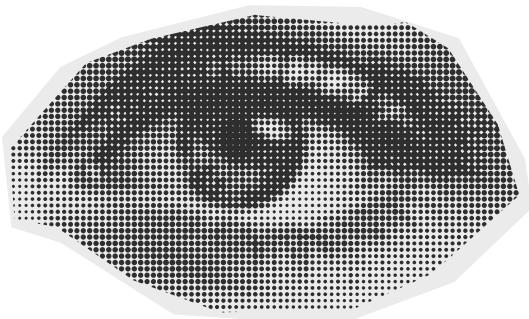
First, we need to understand **what UV radiation really is**. Ultraviolet radiation is a **form of non-ionizing radiation** that is **emitted naturally by the sun** but can also be created **artificially by other sources** such as tanning beds. UV radiation can be classified into **three main types based on their wavelengths: UVA, UVB and UVC**. The latter one is completely walled off by the ozone layer, while **UVA and some amount of UVB** can penetrate through the earth's atmosphere and **can damage our skin and eyes**. However, it can also, in the case of UVB, **help us produce vitamin D**. Now, the amount of exposure a person gets is dependent on several factors such as geographical location, altitude, and time of day. Since **the sun is positioned directly over the equator**, UV rays can penetrate more easily into this zone of earth, effectively making them **harsher on our bodies**. As for altitude, it is worth noting that radiations level **can increase up to 10% per kilometer** of rise in altitude, because there are **fewer radiation-absorbing substances** in the atmosphere to filter the rays out. Lastly, between the hours of 10a.m to 4p.m, the **UV rays are more intense** and more damaging since

that is when the **sun gravitates towards its highest point**. This is **not affected** by the **number of clouds or rain** as much as you would expect. In fact, **some weather conditions can increase** the **amount of UV rays** we are exposed to, **for example snow**, which is a particularly **good reflector** for these rays. [1]

That is all regarding the UV radiation from the sun, but what about **artificial sources**. Fortunately, most sources of artificial UV rays are being phased out, such as **deuterium lamps**, which are much **weaker than the sun**, like **UV lamps**, or are used in very **specific professions**, for example **Ultraviolet lasers used by dermatologists**. However, there is one artificial source that should take precedence over the others, **tanning beds**. Used by many around the world, tanning beds promise a quick and easy body tan for those who want to have one. **Problems arise** however, when we look at the **radiation these devices emit**, which is primarily UVB. It is no wonder that when epidemiological studies in 2012 compared people who used tanning devices and people who did not, they found a 20% **increase in the risk of melanoma**. The risk also seemed to be even **higher for those who have used a tanning device before the age of 35**. Besides the increased risk of melanoma in these people, what studies have also found, is an **increase in the incidence of photokeratitis**, also known as **snow blindness**, and **ocular melanoma**, a type of **eye cancer**. Which brings us back to our topic, how do UV rays affect our eyes? [2]

The **Human eye** itself is made of **three layers of tissue** arranged concentrically. We have the outer layer, which consists of **sclera** and **cornea**, the middle layer named **uvea** and finally the inner layer called **retina**. What is worth noting is that the **uvea is the most vascular** of the layers and **retina is mostly made of nervous tissue** and it's where **light is translated into image**. Externally we have the **eyelids**, the **ocular muscles**, the **accessory glands** and the **conjunctiva**. From all the aforementioned, the cornea, the macula, the retina and the eyelid are the parts of the eye that are **most affected by the UV rays**. You see, the cells of the eye are **constantly regenerating**, especially those located on the lens and retina. The cells on the eyelid on the other hand are like those on the rest of the skin, but the layers here are thinner and as such **cannot block the negative rays** of the sun's as effectively. [5]

UV rays **can penetrate** almost without any difficulty **all layers** of the human eye and since the eye as an organ is constantly regenerating, that means **tumors and mutations can appear** more frequently.

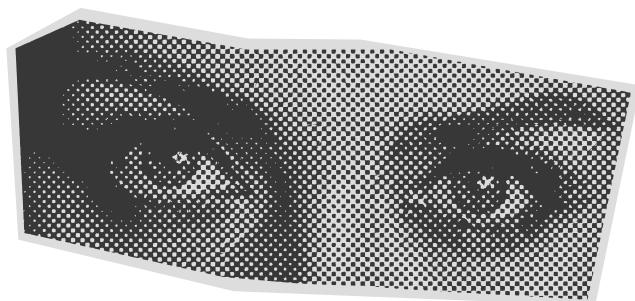


First off, the UV rays hit the outermost layer, the **cornea**, which itself **absorbs quite a big amount of radiation**, particularly **UVB**. This triggers the **production of inflammatory molecules**. Chronic production of those can lead to **photokeratitis**. This **painful condition** causes a sensation of grit in the eye, water, photophobia and temporary blurred vision. You can think of photokeratitis **like a sunburn but for the eyes**. The good news is that, if the damage to the cornea is not extensive, the **epithelium should heal** within one to three days. Another condition related to the cornea is **pterygium**. This is a **fleshy overgrowth over the cornea** that can cause **distortion or loss of vision**. It is more common in people who work or go out in the **midday sun** without any protection. This condition **sometimes requires surgery** to be performed on the eye to restore vision.[1]

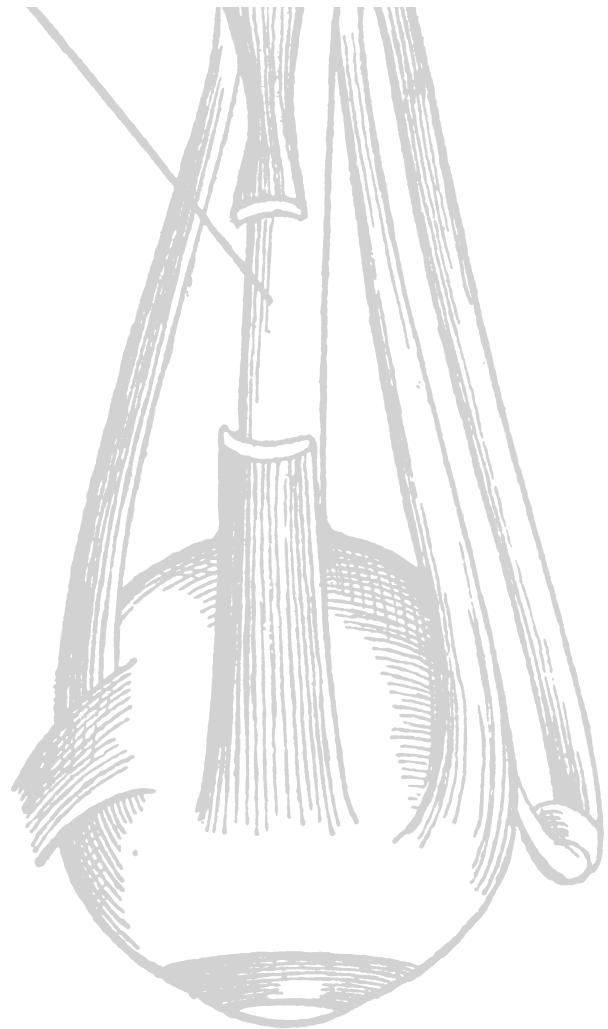
The next part of the eye that can be gravely affected by UV rays is the **macula**, which is a **light-sensitive tissue** responsible for seeing things in your **direct line of vision**. **Macular degeneration** is associated with **chronic exposure to UV rays** and once started, it **cannot be reversed**. Some of the symptoms of macular degeneration include visual distortions, reduced central vision and difficulty adapting to low light levels. It is a condition that ophthalmologists are still trying to find an **effective way to combat**.

Another **common condition** regarding the **lens** is **cataracts** and it has been longed linked to **exposure to UVA rays**, which with their longer wavelength, can penetrate deeper into our eyes and **cause proteins to denature** and clump together, which leads to the **clouding of the lens** we call cataracts. **Blurry vision is the main complaint** from patients and the condition **can only be healed through surgery**.

Finally, UV rays' exposure can cause **uveal melanoma**, a type of **eye cancer affecting uvea**, the pigmented middle layer of the eye. This type of cancer is **usually seen as a dark spot on the iris** that keeps growing. Patients may sometimes be **asymptomatic** but most of the time they have **blurred vision**, eye floaters or loss of peripheral vision. **Complications** of the disease include **retinal detachment**, which if not treated can lead to **blindness**. It is worth noting that uveal melanoma is the **most common type of primary cancers of the eye** and more than half of them **can spread**, mostly to the **liver**. There are treatments such as **proton therapy** and **immunotherapy**, but **prognosis is usually quite poor**, especially if it is not spotted early on. [4]

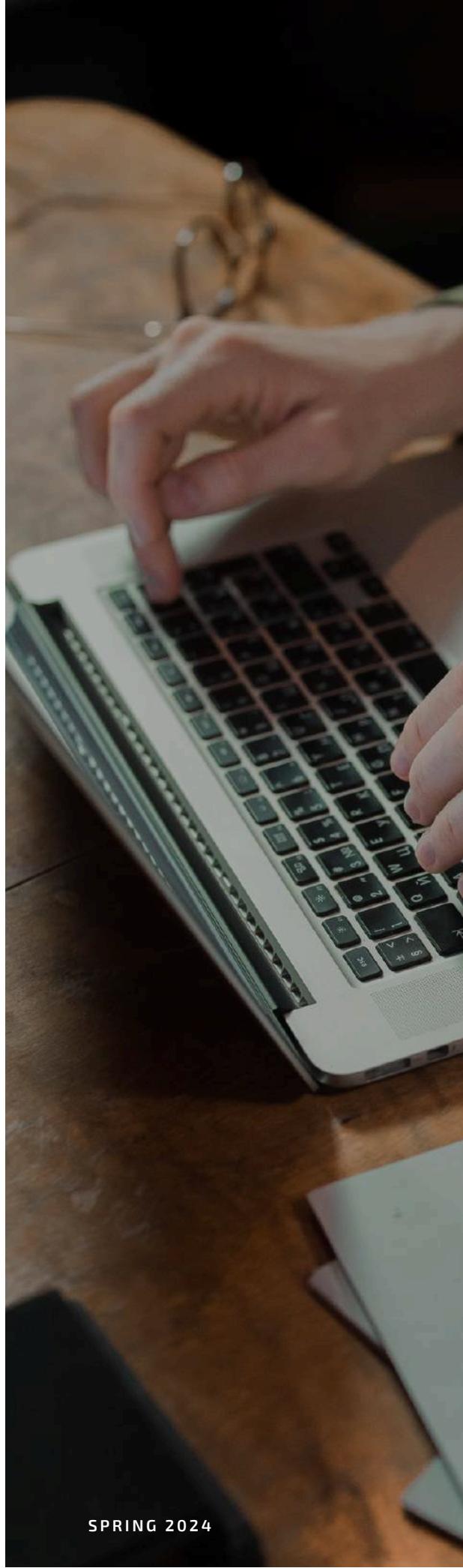


Regarding protection from the sun, we need to understand that, **yes, too much exposure can be harmful**, however **avoiding the sun** completely is **not recommended** either, since it **helps us produce vitamin D** and **reset our circadian rhythm**. What we need to do is take the **necessary precautions** before exposing ourselves to the harmful UV rays, because like we said UVA rays can damage the macula, while UVB are harmful to the lens and cornea. The **number one protection** for our eyes is of course, **wearing sunglasses with a UV400 rating**, with a **large frame** and **wraparound protection**. Beyond that, wearing a **wide-brimmed hat** can also offer some protection from the sun. Secondly, we can try to **limit our midday sun exposure**, when the sun hits the hardest. Finally, **staying cautious near reflective areas**, applying a lot of sunscreens of **at least SPF30+** and **avoiding tanning devices** altogether can help us protect our skin and eyes from the sun. Finally, for people **working with machines like X-rays** and Computer tomographs, take precautions to minimize the exposure to the eyes, which for now they are simply **avoiding the beams**, but soon **lead containing glasses** will be available to all health professionals. [3]



REFERENCES





WRITERS *JOIN US!*

From breaking news to deep dives into specialist topics, join the writing team to explore and share your scientific interests!

JOIN EUC MEDICAL SCHOOLS' FIRST STUDENT-RUN MEDICAL JOURNAL.

[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

Unveiling the Efficacy of Anti-Obesity Drugs

WRITTEN BY ZENA AL-DAKKAK
EDITED BY EMMA ARIFAGIC
DESIGNED BY ANASTASIA LEBEDEVA

Obesity is a **chronic, recurrent, and progressive disease** that presents a **significant public health concern** due to its association with **numerous other health conditions** leading to **disability, mortality, and morbidity**. While lifestyle modifications remain an important form of treatment, it is very **difficult to sustain long-term weight loss**. Alternatively, **bariatric surgery** is a form of treatment that may not be a preferred option for every patient. This review discusses the sufficient evidence supporting that **pharmacotherapy (AOMs)** in combination with **behavior-based interventions** can result in significant **weight loss** and improved **cardiometabolism**. The efficacy and tolerable safety profiles of these drugs aid in the **management of obesity** and reduce the **complications** associated with this **chronic disease**.

In a period where **obesity has become an epidemic** that stands out prominently, the search for **effective treatments** has instigated a large amount of **scientific and medical research**. Apart from **lifestyle changes** such as diet and exercise, many individuals have resorted to these **pharmaceuticals** in hopes of **attaining greater weight management**.



Anti-obesity drugs emerged among the **list of interventions** to have shown **promising results**. However, behind their alluring promises lie a variety of **ethical considerations, dubious efficacy, and potential risks** and benefits. As we dig deep into the topic of anti-obesity drugs, many different **questions** are raised regarding the **medicalization of weight**, the influence of pharmaceutical companies, the **stigmatization** of those who are overweight, as well as clinical efficacy and effectiveness. In this **opinion piece**, an analysis and **discussion regarding certain drugs** that have been approved by the Food and Drug Administration (FDA) for **weight reduction** will be explored. The ones that will be discussed include: **Orlistat, Bupropion/Naltrexone combinations, and Liraglutide**.

The term **medicalization** is often **largely misunderstood** due to its vast context and subjectivity. According to one definition, it is a **process by which non-medical problems become defined and treated as medical problems**, usually in terms of illness or disorders'. As perceived by different groups, medicalization has allowed a form of **medical dominance** over every dimension of being and is viewed as **a type of social control**.

whereas others perceive it as a **venture of sociology into medicine**. In this opinion piece, medicalization is interpreted as a **process in which a non-medical issue, body fat, is analyzed in medical terms in which diagnostic tools, studies, and solutions are used for evaluation and treatment** (5). The clinical definition of **obesity**, according to the Centers for Disease Control and Prevention (CDC), is any adult with a **BMI of 30 or higher** (4). Obesity has surfaced as a **widespread global issue**, with adult prevalence **exceeding 40%** and said to escalate further post the **COVID-19 pandemic**. While there are **numerous factors** that may **influence obesity**, one's **lifestyle choices** remain the **biggest contributor**. It was believed to be an **illness of industrialized countries**, however, it is evident now that **obesity affects both underdeveloped and developed countries** due to poor nutrition and sedentary habits. As the pandemic grows, it is said that the **economic burden of obesity** is set to increase drastically, **reaching \$48-66 billion in medical costs** by 2030. As previously mentioned, the key towards **treating obesity** begins with **lifestyle changes** such as a **good exercise routine** and a **healthier diet**. Randomized trials were conducted in which a **>8% decrease in weight** was noted in those who followed this kind of treatment. However, cumulative data suggested that **this kind of lifestyle is not sustainable** as more than half of those patients **regained the weight they lost within two years**.

Anti-obesity medications (AOMs) are designed to **assist** individuals who **struggle to lose weight through lifestyle changes**, yet the available **treatment choices** are **restricted**. Several medications have been pulled from the market due to **adverse psychiatric or cardiovascular effects**. After the removal of **sibutramine**, the Food and Drug Administration (FDA) mandated **placebo-controlled cardiovascular safety trials for new anti-obesity drugs**. These required trials yielded encouraging outcomes for obesity management (3).

To begin with, **Orlistat**, a **gastrointestinal lipase inhibitor** that is considered to be a globally sanctioned medication for long term weight control, functions by **reducing lipid absorption**. It achieves that by **slowing down the breakdown of dietary triglycerides** into absorbable **monoglycerides** and **free fatty acids**, thus supporting a **deficit in calorie intake** without any impact on appetite. Considering its mechanism of action, Orlistat is **more suitable for those who tend to eat fatty food** and is expected to have greater weight-loss effects in them than in those with non-fatty food consumption habits (1). Randomized controlled trials (RCTs) involving Orlistat have shown a **5-10% reduction in weight in patients with obesity**, exceeding the effectiveness of a placebo with doses extending from 30 to 240 mg. Additionally, a one-year study demonstrated that 9.1% of individuals treated with Orlistat attained a **>20% decrease in their body weight** as opposed to 6.1% of

those who received a placebo. **Orlistat is generally deemed safe**, with most concerns involving its **tolerability**. The most common adverse effects recorded were **mild to moderate gastrointestinal issues**, occurring in up to 91% of those in their first year of treatment, and 36% after four years. Other symptoms including **fecal incontinence, flatulence**, and **steatorrhea** typically **improved with a low-fat diet**. Long-term cardiovascular safety data for orlistat are **unavailable**, and no trial was specifically designed to assess these factors. Nonetheless, **no deaths were attributed to orlistat** use during the four-year study period (2).

As for the **combination of Naltrexone and Bupropion (NB)**, it has been available for managing obesity chronically in the US and Europe since 2014. **Naltrexone** acts as an **opiate receptor antagonist**, while **Bupropion inhibits dopamine and noradrenaline reuptake**. The exact mechanism by which Bupropion decreases appetite is **not fully understood**, however, some theories suggest that it might **diminish food reward** or directly **influence the hypothalamus to enhance satiety**. Naltrexone on its own is **not as clinically efficacious** in terms of significant weight loss - although when combined with Bupropion, it elicits synergistic effects on rewarding pathways, **thus decreasing food intake** and allowing for greater weight loss as opposed to the **use of Bupropion alone**.

Obese patients who received **NB (32mg / 360 mg)** along with a hypo-caloric diet (500 kcal deficit per day) and increased physical activity over 56 weeks, **achieved an 8.1% reduction in body weight** in comparison to a 1.8% decrease that was recorded in the placebo group. Moreover, **NB has proven to be efficacious** in obese patients diagnosed with type 2 Diabetes Mellitus (T2DM). As for the adverse events in NB treatment, the most common ones were listed as **nausea, headaches**, and **constipation**. While **cardiovascular safety requires further investigation** through RCTs, a recent systematic review and meta-analysis revealed **no link between the use of naltrexone, bupropion**, or their combination and the occurrence of **major cardiovascular adverse events** when compared to placebo (2).

Glucagon-like peptide 1 (GLP-1) is a **hormone** found in the **intestines** that plays a role in both **regulating feelings of fullness** as well as adjusting **blood glucose levels**, hence its incretin function. It is able to **decrease appetite and food consumption** by exhibiting **satiety signals** in the brain, thus directly affecting areas such as the **hypothalamus, vagal nerve stimulation**, and other neural pathways. An example of a GLP-1 is **Liraglutide**, a drug approved for treating **T2DM**.

Liraglutide has also been widely sanctioned for **obesity management** in those with **BMI \geq 30 kg/m²**. In an RCT involving **adolescents with obesity**, treatment with Liraglutide demonstrated a **much greater reduction in BMI** compared to a placebo in which 43.3% versus 18.7% achieved at least a 5% decrease in BMI, while 26.1% versus 8.1% experienced a reduction of at least 10%. The **SCALE** (Satiety and Clinical Adiposity—Liraglutide Evidence) **programme** comprising clinical trials in four phases assessed **the use of liraglutide and weight loss in individuals with and without diabetes**. A double-blind RCT evaluated **3.0 mg of liraglutide** in the treatment of obesity for 20 weeks ($n = 564$). Results showed **greater weight loss over orlistat** and placebo, and decreased body fat by 15.4% and lean mass by 2% after 20 weeks of treatment. Moreover, it **resulted in sustained weight loss**, as >85% of the patients with a >5% body-weight loss in the first year maintained that loss in the second year (2). Liraglutide is **deemed safe**, and its side effects including **nausea, vomiting, diarrhea, constipation, and dyspepsia** were reported to be **manageable** by most patients over time. However, a recent meta-analysis discovered that among all the FDA-approved anti-obesity medications, **liraglutide had the highest rate of discontinuation**, a recorded 13% of study participants due to its side effects, followed by naltrexone/bupropion with a 12% of study participants (1).

Additionally, **when compared with other anti-obesity drugs**, one of the main benefits of liraglutide is that it has **no contribution to the incidence of CVD** in obese patients with T2DM (2).

Although **obesity is considered a chronic condition** with numerous health implications and a shortened lifespan, it is **often inadequately addressed**. A variety of factors add to the **underutilization** and **stigmatization** of **AOMs**. What commonly leads to the premature discontinuation of treatment is the **modest typical weight reduction** which falls below the expectations of both the patient and physician, respectively. Furthermore, **some medications have been banned** due to their associated health risks causing hesitation amongst potential users.

However, it is important to note that **in order for AOMs to reach their full potential**, a shift in the perception of obesity as a chronic condition requiring ongoing clinical management must take place. **Only then can AOMs assume a significant and widespread role** in disease control and overall health improvement for individuals with obesity, while **bariatric surgery** remains relevant for **severe cases** or non-responsive patients (2). An analysis regarding AOMs' safety data, long-term usage, weight reduction (%), and comorbid diseases in patients with obesity was established.

Due to the **drastic increase in morbidity and mortality of obesity**, the use of **pharmacological treatment** in conjunction with physical activity and healthier eating **should be considered for those with a BMI $\geq 30 \text{ kg/m}^2$** and an obesity-related comorbidity. Data extracted from the most recent meta-analyses demonstrated that the **overall placebo-subtracted weight reduction (%)** with the use of **AOMs** for at least 12 months ranged from 2.9 to 6.8%: liraglutide (4 trials, 5.4%), naltrexone/bupropion (5 trials, 4.0%), and orlistat (17 trials, 2.9%) (1). With larger **implementation of these drugs**, global **obesity burden** may **diminish** and **type 2 diabetes** can be **prevented**.



REFERENCES





EDITORS *JOIN US!*

Read about a wide variety of scientific topics and help edit articles for greater clarity by joining our editing team!

JOIN EUC MEDICAL SCHOOLS' FIRST STUDENT-RUN MEDICAL JOURNAL.

[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

IMMUNE CHECKPOINT INHIBITORS IN HIV INFECTION

A Potential Therapeutic Opportunity?

Immune checkpoint inhibitors (ICIs) have transformed cancer treatment by blocking tumor-mediated immune inhibition, leading to a **proinflammatory tumor microenvironment**. Interestingly, similar **immune exhaustion patterns** observed in oncologic patients were found in **people living with HIV/AIDS (PLWHIV)**, suggesting a potential treatment avenue for HIV. T cell exhaustion, a hallmark of both chronic HIV infection and various cancer types, presents a challenge to effective immune response. Despite significant advancements in **antiretroviral therapy (cART)**, which suppress viral replication, **HIV reservoirs** persist due to sustained immune activation. **Checkpoint receptors** such as **CTLA-4 and PD-1** play crucial roles in immune dysregulation during chronic HIV infection, offering targets for therapeutic intervention.

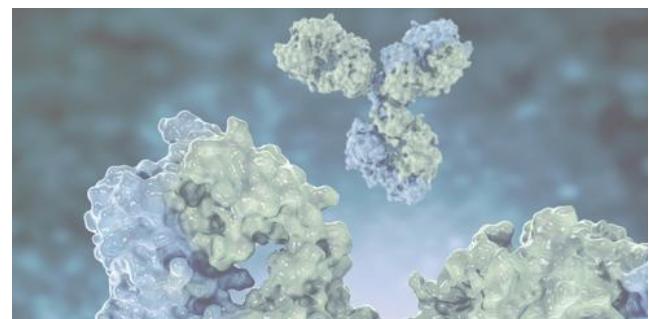
Combination therapy involving multiple checkpoint inhibitors in parallel with cART, notably **anti-PD-1 and anti-CTLA-4 antibodies**, has shown remarkable efficacy in cancer treatment and holds potential for HIV cure or remission. However, **further research** is needed to elucidate optimal combinations.

WRITTEN BY ANTONIOS PAPASAVVAS

EDITED BY JACALINE SKOUROS

DESIGNED BY NOORA ALKETBI

Immune Checkpoint Inhibitors (ICI) are monoclonal antibodies used for several years now as a part of **antineoplastic therapy** for various cancer subtypes. **Programmed death-1 (PD-1)** and **cytotoxic T lymphocyte antigen-4 (CTLA-4)** are proteins found on lymphocytes. These interact with ligands on the cell surface of **antigen presenting cells (APC)** or cancer cells (**PD-L1/2 and CD80/86**), causing the release of stimulatory or inhibiting signals (1). **CTLA-4** is present on **helper T cells (CD4+)** and **Cytotoxic T cells (CD8+)** lymphocytes and binds to its ligand on antigen-presenting cells (APCs) causing reduction of **interleukin-2 (IL-2)** production and **T-cell proliferation** (1). **PD-1** is a receptor expressed on the cell membrane of **T cells, B cells** and **NK cells**. **PD-L1**, its ligand, is present on multiple cell types including tumor cells, causing **inhibition of activated T cells** (1).

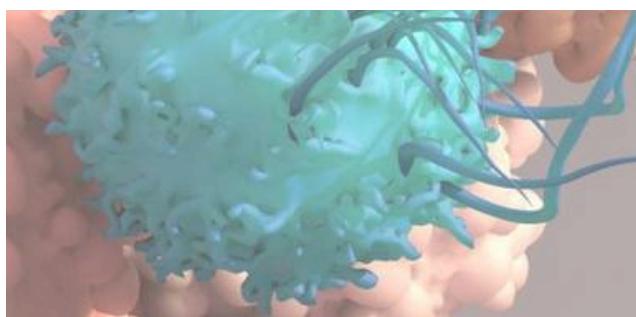


With the use of **ICIs**, the **tumor-mediated immune inhibition** is blocked, leading to a **proinflammatory tumor microenvironment**, triggering an **inflammatory-mediated toxicity** for disease control (1).

Despite the fact that **ICIs** have been used in cancer treatment, it was observed that the **T cell immune response** of **PLWHIV** resembles the immune exhaustion observed in oncologic patients. This was a sign that **ICIs** could be potential treatment for PLWHIV (2).

T cell exhaustion is something that is observed both in **PLWHIV** and in a variety of cancer types. Several stimuli can cause T cell exhaustion; T cells are **unable to perform** their **normal functions**. This can lead to the deletion of **antigen-specific** T cells and further inability of T cells to **control and eliminate infected or neoplastic cells** (2).

In the case of **HIV infection**, in patients with **persistently high viremia**, a loss of immune control of viral replication occurs. In the **initial stages**, there is a **partial suppression of HIV viral replication**, but with persistent high levels of viral charge, **T cells lose their ability to efficiently kill** the infected cells, due to **exhaustion** (2).



After the **recent involvement of PLWHIV in studies with ICIs**, it is found that this type of treatment could be candidates for the **shock and kill strategy**; activate the latent reservoir (shock) to enable HIV-specific immunity to recognize and eliminate (kill) infected cells and effectively **remove the reservoir** (2).

The use of **ICIs** have revolutionised the field of **oncology**. **PLWHIV** have only partially benefited from this revolution, **as they have been excluded** from multiple trials in the past that included ICIs (3).

Antiretroviral therapy (cART) has been used for **many years** now, aiming to **decrease the viral charge**, but not being able to eliminate the **HIV reservoirs**. This persistent viral infection contributes to a **sustained inflammatory environment** that promotes the **accumulation of exhausted T cells** that are unable to kill the infected cells (3).

The best studied checkpoint receptors in the context of HIV are the **CTLA-4 and PD-1**. **Lymphocyte activation gene (LAG3)**, **T cell immunoglobulin and ITIM domain (TIGIT)** and **T cell immunoglobulin and mucin containing 3 (TIM3)** are not well defined in the pathogenesis of the infection (3).

Checkpoint receptors are expressed in **HIV-specific T cells and latently infected CD4 T cells**. In chronic HIV infection, cells of the **adaptive immune system** become dysfunctional and express an abnormal number of checkpoint receptors that **block the HIV-**

specific responses (3).

The **main challenge** when it comes to HIV treatment is to **eliminate the viral reservoir**, which is established **very early in the infection**. Recent studies have demonstrated that **multiple immune checkpoint receptors are expressed** by latently infected cells; an additional challenge to overcome by the **HIV-specific CD8+ T cells**. This also happens in patients with **suppressed viremia by cART**, where T cells also express checkpoint receptors such as PD-1, TIGIT and LAG3 and **contain ten-times more HIV-DNA** than the checkpoint receptor negative CD4+ T cell counterparts (3).

Pre-clinical in vitro studies have shown contribution of **PD1 engagement** in the establishment of **HIV latency**. In these conditions, **inhibition of PD1/PD-L1 pathway with anti-PD1** led to a significant **decrease** in latently **infected cell numbers**. In the contrary, other reports have shown **small effects on viral replication** in an ex-vivo stimulation of CD8 in the presence of anti-PD-L1 or anti-PD1. Another report showed that **reversal of HIV latency** was achieved by **blockade of the checkpoint receptors** without, though, T cell stimulation, finding significantly **higher effects than using latent reversal agents** (3).

The effect of **ICIs** for the treatment of HIV is **under investigation**. The inhibition of the checkpoint inhibitors **can restore immune function** and recent studies showed that they can act as **latency reversal** agents to activate

the **reservoir** in infected cells. While the immune mechanisms is similar in **chronic HIV infection** and in **cancer**, the exhaustion of HIV-specific T cells seems to be **more difficult to reverse than in the cancer setting**. It is shown that transcriptional and epigenetic factors on **exhausted T cells** contribute to this difference and therefore to the **limited response** to the checkpoint receptor blockade. This suggests that **duration of infection, chronic immune activation and expression** of several checkpoint receptors may cause **limited plasticity in HIV-specific T cells**. Further investigation is required to overcome these challenges, whether T cells at **early stages of the HIV infection** are more susceptible to **reverse exhaustion**, or combination of several checkpoint receptors **will achieve better results** (3).

Antiretroviral therapy (cART) has **dramatically improved life expectancy** for **PLWHIV** and helps to **restore immune function** but is **not curative** and must be taken lifelong. Achieving long term control of HIV in the absence of ART will likely require **potent T cell function**, but chronic HIV infection is **associated with immune exhaustion** that persists even on cART.



This is driven by **elevated expression of immune checkpoints** that provide negative signalling to T cells. In individuals with cancer, **immune checkpoint blockade (ICB)** augments tumour-directed T-cell responses resulting in **significant clinical cures**. There is therefore high interest if ICB can contribute to **HIV cure or remission** by reversing HIV-latency and/or drive recovery of HIV-specific T-cells. Recent evidence on the role of immune checkpoints in persistent HIV infection discuss the **potential for employing immune checkpoint blockade** as a therapeutic approach to target HIV persistence on cART (4).

Combining immune checkpoint blockade, notably with **anti-PD-1 and anti-CTLA-4** antibodies, has shown **remarkable therapeutic efficacy** in clinical trials, particularly in treating melanoma and **potentially in HIV**. This **combination therapy** has led to improved **long-term survival rates** for patients, while accompanied by **higher rates of immune-related toxicities**. The success of this approach stems from its ability to **independently target PD-1 and CTLA-4 signalling pathways**, which regulate **T-cell activity**.

This **attenuation** of T-cell activity, achieved through separate mechanisms, may underlie the **enhanced treatment outcomes** observed with combination therapy. **Preliminary data** suggest a **potential synergy** between PD-1 and CTLA-4 blockade, particularly in **reversing latency in HIV**, although the exact mechanisms remain **unclear**.

It's posited that engagement of distinct **T-cell populations** by anti-CTLA-4 and anti-PD-1 antibodies could **contribute** to this **enhanced effect**, as these antibodies may have **complementary effects** on T-cell function and immune response. Furthermore, studies have shown that **combining blockade** against multiple immune checkpoints can lead to **enhanced cytokine production** and **T-cell function**, particularly when antibodies targeting additional checkpoints like **LAG-3, CTLA-4, and TIGIT** are included. However, **more research** is needed to elucidate the **optimal combinations** of immune checkpoint inhibitors and their mechanisms of action. Additionally, efforts are required to **determine how to administer** these combinations safely to minimize immune-related toxicities while **maximizing therapeutic efficacy** (4).

Pre-clinical data have shown that **ICB** could be a **potential cure** for PLWHIV. Studies on PLWHIV have shown the **reversing effect on HIV latency** in the presence of **ICIs** and even clearer results are shown in the **combination of cART and ICIs**. The simultaneous blockade of more than one inhibitory pathways, while superior to **single-agent blockade**, could lead to **increased toxicity** and further investigation is needed to **find the balance** (4).

REFERENCES





DESIGNERS *JOIN US!*

Enhance your creativity by bringing the authors' and editors' words to life as part of the design team!

JOIN EUC MEDICAL SCHOOLS' FIRST STUDENT-RUN MEDICAL JOURNAL.

[LINKTR.EE/EDGEOFMEDICINE](https://linktr.ee/edgeofmedicine)

IS IT FOR YOU?:

Impacts of a Ketogenic Diet on Sports Performance

WRITTEN BY ELIAS ZREIQ
EDITED BY BANO IMTIAZ
DESIGNED BY APHRODITE P. PASCOE

In the twenty-first century, the popularity of the ketogenic diet has dramatically increased

Alongside the increase in popularity came an increase in research, particularly in relation to athletic performance. This piece delves into the impacts of the ketogenic diet on both anaerobic and aerobic exercise, evaluating parameters such as fat mass, fat-free mass, strength, and performance. In relation to the evaluated parameters, studies evaluating anaerobic exercises, specifically resistance-training, showed mixed results; studies evaluating aerobic exercises showed a generalized positive trend in outcomes. Regardless of the wide array of findings in studies, one pattern could be identified: reductions in fat mass. The adaptation of the ketogenic diet should revolve around athletes' specified and individualized goals. Additionally, the ketogenic diet can be tailored to the specified and individualized goals of athletes: such as augmenting protein intake levels. Consulting medical professionals is also advised, in order to conclude safety and efficacy of suitability and alteration tactics, - as best as possible. Further research is required in order to better understand the relation of the ketogenic diet on athletic performance.

Within 380 milliseconds, a Google search of the term "Keto Diet" returns 270,000,000 results. The first page, and often the only one visited, is mostly filled with "guides for beginners" and "is it for you" articles. This, then, ultimately raises the question: is it for you? This comes in parallel with a number of other questions that someone must ask themselves before choosing to indulge in a new routine of eating.

The Harvard School of Public Health describes the ketogenic diet as one that revolves around a low-carbohydrate, high-fat eating style which has been used as intervention for different medical conditions throughout history: diabetic control; epilepsy in children who did not respond to medication; cancer, polycystic ovary syndrome, and Alzheimer's (1). The structure of the diet is not definite, but the parameters involve a high concentration of fat, a lower concentration of protein, and a depletion in carbohydrates (20-50 grams/day, with a daily intake of 2,000 calories); this allows for a shift in the source of energy production and molecules for expenditure to occur: from carbohydrates and glucose to fat and ketones. In order for this shift to occur, the body needs to be depleted of its glucose storages. The depletion of the storages varies in time from person to person, but

has an average duration of three days to a week. During this transition stage, people tend to experience a range of symptoms such as hunger, fatigue, low mood, headaches, and brain fog, - this is termed as the "Keto-Flu" (1,2). This piece will take a look at the impact of the ketogenic diet on sports performance while addressing possible hindrances experienced due to the Keto-Flu.

As of 2024, a mixture of aerobic and anaerobic sports make up a majority of the top ten sports played globally (3). Aerobic sports are forms of exercises which involve the metabolic pathway that relies on oxygen in order to extract adenosine-triphosphate (ATP) to be used as energy. These forms of exercise, -running, swimming, cycling -, rely heavily on the cardiovascular system for the provision of oxygen (4). Anaerobic sports are forms of exercises which involve the metabolic pathway that is independent of oxygen. ATP is derived in the cytoplasm of cells through glycolysis. Anaerobic sports consist of exercises, - sprinting, high-intensity-interval training (HIIT), and power-lifting -, that require fast muscular twitching to occur (4). In order to cover a wide array of sports, this piece will take a look at the impact of the ketogenic diet on sports from a perspective of aerobic and anaerobic exercise types.

A majority of the studies conducted in relation to anaerobic exercise focused on resistance training, specifically weight-lifting. As a result, the main parameters measured were fat-free mass, lifting performance and strength, and body fat. In Vargas-Molina et al., the study lasted for a duration of six weeks, therefore focusing on the more immediate impacts and results of a ketogenic diet's effect on trained athletes. The study showed that there was no loss in resistance training performances and strength, apart from the period of the keto-flu, in the early periods of the low-carbohydrate intake diet. After the keto-flu, the lifting performance and strengths returned to normal; emphasizing the six week study period reminds us that measurements of increased muscle mass and lifting powers could not reliably be measured (5).

Another systematic review and meta-analysis, focusing on fat-free mass, by Vargas-Molina et al. was conducted. This review had an inclusion criteria for studies with a duration of at least eight weeks, - allowing for more reliable fat-free mass measurements. The research showed, also, that overall there were no significant differences in fat-free mass between the control and study groups. Although, conclusions from the paper stated that an increase in fat-free mass would be possible under the circumstances that satiety was not so easily reached while undergoing a ketogenic diet.



The relation between a ketogenic diet and satiety is the higher intake of fat and protein, which has been seen, in other studies, to induce a quicker feeling of satiety compared to macro-balanced intake diets. This conclusion was drawn as a result of conflicting results found in works they analyzed: some showing significant decreases in fat-free mass in athletic participants undergoing a ketogenic-diet and some showing significant increases in non-athletic participants (6). In another study by Koerich et al., the conclusion showed a significant difference in fat-free mass: there was a strong favoring of those on a carbohydrate-oriented diet; in comparison, the ketogenic-diet favored fat loss . One must consider that the participants in this study did not primarily focus on strength training, but also on cycling (7). In addition, a study by Paoli A. et al. revolved around a group of natural bodybuilders who underwent a ketogenic-diet for eight weeks, in comparison to a control group undergoing a normal Western Diet. The results showed sustained muscle mass with a significant decrease in body fat. Although the control group following the Western Diet experienced significant increases in lean-muscle mass, there was an equal increase in maximal strength in both groups (9). In a study by Greene DA. et al., powerlifting and olympic weightlifting athletes underwent a ketogenic-diet for three months, a two-week washout period, and a usual diet for three months,- in random order.

This study showed a significant decrease in body mass and lean mass during the phase of the ketogenic-diet, but retained lifting strengths in comparison to the period of a usual-diet (10).

Studies focused on aerobic exercises showed more promising results in relation to a ketogenic-diet. A study by Gregory RM. et al. on crossfit trainers undergoing a ketogenic diet for six weeks resulted in the athletes maintaining their lean-body mass while improving performance outputs and significantly decreasing their body-fat percentages (8). A study by Paoli A. et al. stated that endurance athletes always react differently to ketogenic-diets, but in relation to endurance and off-road cyclists in this study, there were no negative effects observed while undergoing a ketogenic-diet (11). A study by Moreno-Villanueva et al. observed that in their search, the ketogenic-diet played no significant changes in performance of endurance athletes, - although one reviewed study suggested a decrease in body weight and increases in maximum ventilated oxygen measures, insighting positive effects. In addition, the study found that athletes felt an increase in peak power and a decrease in effort exertion (12). The one study which resulted in decreased performance was by Zinn C. et al.



Five athletes were observed for an intervention period of ten weeks: the athletes experienced decreased performance levels; a decrease in body fat; decreased energy levels during the time of the keto-flu with a return to higher levels than before, once it passed; and an enhancement in recovery (13).

Taking into consideration all of the results from the different perspectives of aerobic and anaerobic exercise in relation to the ketogenic-diet, the results were continuously scattered with difficulty in analyzing and generating patterns. The one outstanding pattern that does, very clearly, present itself is a pattern of reduced fat-mass. This could be due to the combination of having a different mechanism of consuming fat as fuels and a decreased caloric intake, as well as a high energy expenditure that is present in athletes. In relation to the anaerobic exercises, the results varied throughout every single aspect; focusing on fat-free mass though, it seems that most studies showed maintenance of the mass. When fat-free mass is approached in relation to anaerobic exercises, results of improved and increased fat-free mass surface. Could it be that anaerobic exercises play a role in increasing the fat-free mass when on a ketogenic diet? Regardless, all studies mention that further exploration and research is required when exploring the potential intervention of the ketogenic-diet in relation to athletics and their performances.

So, then, this raises the question: is it for you? Should someone involve themselves in a ketogenic-diet? Well, as with every single intervention that someone takes, a person must first ask themselves: what is my goal/what am I trying to achieve, prior to starting. This will allow for a more pinpointed and targeted approach to the intervention in itself. As the studies show, if a person is looking to lose fat-mass, then the ketogenic diet can definitely be an option. If a person is attempting to build fat-free mass or increase endurance capabilities, it may not be the most ideal option. Nevertheless, it cannot go unsaid, that the ketogenic-diet can be altered in specific ways to accompany varying goals of a person: increasing intake of protein to higher levels, for example. But in doing so, one must always consult their medical health professional to accommodate and adapt in ways which will not impose any risks/harms upon themselves. The potential of the ketogenic-diet is valid, but applying the basis of it and manipulating it to a person's liking could prove to be of most benefit.



REFERENCES



EDGE OF MEDICINE

