Universidad Europea

GRADUATION PROJECT

Degree in Dentistry

TRIGEMINAL VIRAL INFECTIONS

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ABSTRACT

Introduction: Infections of the trigeminal nerve are a major cause of neuropathic pain and orofacial disease. This study focuses on a complication of the varicella-zoster virus, postherpetic neuralgia (PHN). PHN is a chronic neuropathic condition that occurs after the reactivation of the varicella-zoster virus, affecting the sensory distribution of the trigeminal nerve. It is one of the most debilitating complications of herpes zoster, particularly in immunocompromised patients and the elderly; **Objectives:** This work aimed to determine how treat and manage as efficiently possible the postherpetic neuralgia; **Methods:** A literature review was conducted using databases such as PubMed, Scopus, and the CRAI Dulce Chacon library to find recent and relevant articles on postherpetic neuralgia and how to treat it. Articles within the past 10 years and in English, French and Spanish were considered; **Results:** The results were analyzed, respecting the inclusion and exclusion criteria, a total of 10 articles were selected to discuss what is the best way of treatment and management for PHN; **Conclusions:** Among the numerous available treatments for Postherpetic neuralgia, a multimodal approach combining pharmacological therapies and interventional procedures appears most effective in reducing pain while minimizing adverse effects. However, management must be individualized, as there is no single standard treatment; factors such as patient age, immune status, history of PHN recurrence, and pain response must all be considered to optimize outcomes.

KEYWORDS

Dentistry, post-herpetic neuralgia, treatment, trigeminal infection

RESUMEN

Introducción: Las infecciones del nervio trigémino son una causa importante de dolor neuropático y enfermedades orofaciales. Este estudio se centra en una complicación del virus varicela-zóster, la neuralgia postherpética (NPH). La NPH es una condición neuropática crónica que ocurre tras la reactivación del virus varicela-zóster, afectando la distribución sensorial del nervio trigémino. Es una de las complicaciones más debilitantes del herpes zóster, especialmente en pacientes inmunocomprometidos y personas mayores; **Objetivos**: Este trabajo tuvo como objetivo determinar cómo tratar y manejar de la manera más eficiente posible la neuralgia postherpética; **Metodología:** Se realizó una revisión de la literatura utilizando bases de datos como PubMed, Scopus y la biblioteca CRAI Dulce Chacon para encontrar artículos recientes y relevantes sobre la neuralgia postherpética y su tratamiento. Se consideraron artículos de los últimos 10 años y en inglés, francés y español; **Resultados:** Los resultados se analizaron respetando los criterios de inclusión y exclusión; se seleccionaron un total de 10 artículos para discutir cuál es la mejor forma de tratamiento y manejo de la NPH. **Conclusiones:** Entre los numerosos tratamientos disponibles para la neuralgia postherpética, un enfoque multimodal que combine terapias farmacológicas y procedimientos intervencionistas parece ser el más eficaz para reducir el dolor y minimizar los efectos adversos. Sin embargo, el manejo debe ser individualizado, ya que no existe un tratamiento estándar único; deben considerarse factores como la edad del paciente, el estado inmunológico, la recurrencia de la NPH y la respuesta al dolor para optimizar los resultados.

PALABRAS CLAVE

Odontología, neuralgia postherpética, tratamiento, infección trigeminal

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ABBREVIATIONS

VZV: Varicella Zoster Virus

HSV: Herpes Simplex Virus

PHN: Post-Herpetic Neuralgia

WHO: World Health Organization

PCR: Polymerase Chain Reaction

BCSFB: Blood-Cerebrospinal Fluid Barrier

BBB: Blood-Brain Barrier

CNS: Central Nervous System

DNA: Deoxyribonucleic Acid

EBV: Epstein-Barr Virus

CMV: Cytomegalovirus

IM: Infectious Mononucleosis

PRF: Pulsed Radiofrequency

PVB: Paravertebral Block

ESPB: Erector Spinae Plane Block

STSCS: Short-Term Spinal Cord Stimulation

fMRI: Functional Magnetic Resonance Imaging

GB: Gabapentin

GBP: Gabapentin and Pregabalin

SR: Sustained Release

IR: Immediate Release

V1: First branch of the trigeminal nerve

V2: Second branch of the trigeminal nerve

V3: Third branch of the trigeminal nerve

1. INTRODUCTION

1.1. Overview of the trigeminal nerve

1.1.1 General anatomy of the trigeminal nerve

The trigeminal system is composed of three main components: the trigeminal nerve with its three main branches, the trigeminal ganglion, which houses the nerve cell bodies, and finally the trigeminal nuclear complex, consisting of the mesencephalic, principal, and spinal nuclei. The trigeminal system mediates thermoception, mechanoreception, and proprioception, and plays a central role in detecting nociceptive signals originating from the orofacial area (1,2). The trigeminal nerve is the fifth nerve in the human body, and it is the largest of all. It primarily provides sensory innervation to the mucous membranes and plays a sensory role in various parts of the head. Different areas of the face are innervated by this nerve, depending on its branches: the ophthalmic branch (V1), the maxillary branch (V2), and finally the mandibular branch (V3), each innervating a specific area of the face (Figure 1). It is often essential to know the exact location of the trigeminal ganglion to treat infections involving the trigeminal nerve. The trigeminal ganglion, also known as the Gasserian or semilunar ganglion, is in the trigeminal fossa (called Meckel's fossa), surrounded by cerebrospinal fluid and enclosed by two dura mater layers. The ganglion also contains the cell bodies of the sensory root of the trigeminal nerve (3).

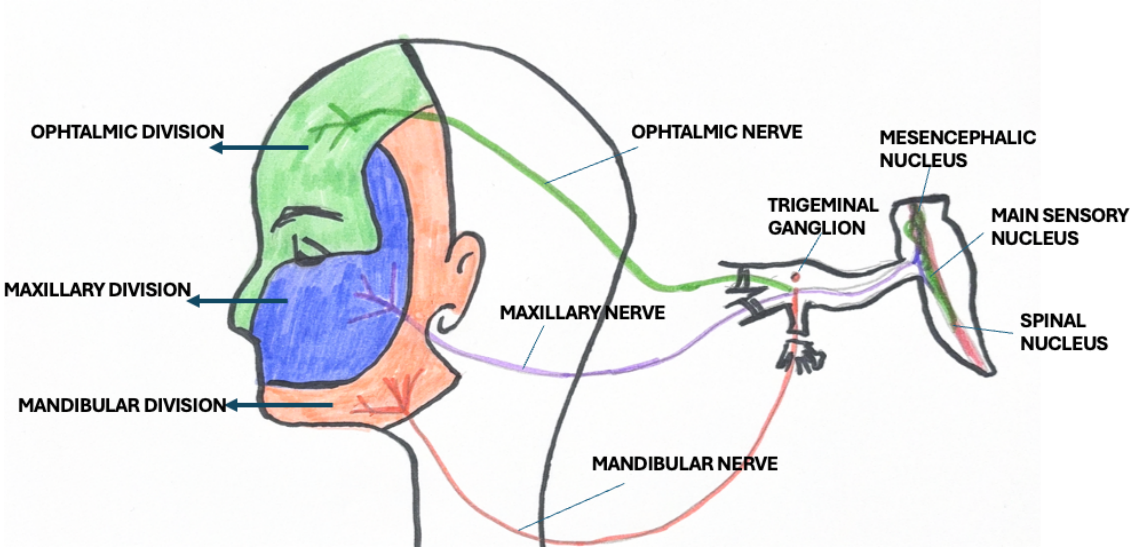


Figure 1: Anatomical organization of the trigeminal system, source: personal work

1.1.2. Divisions of the trigeminal nerve

As we know, the trigeminal nerve is divided into three parts (Figure 2). The ophthalmic branch (V1) is the smallest of the three divisions. It carries somatic sensory fibers, parasympathetic fibers originating from the pterygopalatine ganglion, and sympathetic fibers derived from the carotid plexus. This division innervates the upper part of the face, providing sensory innervation to the forehead, scalp, upper eyelid, and conjunctiva, including the cornea. It also supplies intracranial structures such as the anterior cranial fossa, the falx cerebri, the tentorium cerebelli, portions of the parieto-occipital region, and the dural venous sinuses. After exiting the skull via the superior orbital fissure, the ophthalmic nerve divides into three main branches: the frontal, nasociliary, and lacrimal nerves, which collectively contribute to sensory innervation of the forehead and surrounding regions (2,4,5).

The second branch, the maxillary branch, only has sensory functions. Anatomically, it can be compared to a flattened strip. The maxillary division (V2) exits the cranial cavity through the foramen rotundum and enters the pterygopalatine fossa, where it gives rise to several branches, including the zygomatic nerve, posterior superior alveolar nerves supplying the upper teeth, meningeal branches to the dura mater, and contributions to the pterygopalatine ganglion. Continuing anteriorly, V2 passes into the orbit via the inferior orbital fissure, where it becomes the infraorbital nerve. It then travels along the floor of the orbit and emerges onto the face through the infraorbital foramen, where it divides into terminal branches, namely the inferior palpebral, lateral nasal, and superior labial nerves. Functionally, the maxillary division provides sensory innervation to the midfacial region, including the lower eyelid and conjunctiva, the lateral aspect of the nose, the upper lip, and the cheek. It also conveys sensory input from deeper structures such as the maxillary teeth and gingiva, the mucosa of the maxillary sinus, as well as the hard and soft palate. Additional sensory territories include parts of the nasopharynx and associated glands (2,4–6).

Finally, the last branch of this nerve is the mandibular division, which is the largest of the three. It is a mixed branch: It carries both sensory and motor fibers, as well as parasympathetic fibers that supply the salivary glands. Sensory fibers supply the mandible, lower teeth and gingiva, lower lip, and the anterior two-thirds of the tongue. In addition, V3 conveys sensory input from portions of the temporal region, part of the auricle, and a limited area of the dura mater. Its motor component innervates the muscles involved in mastication.

V3 exits the cranial cavity through the foramen oval to enter the infratemporal fossa, where it divides into anterior and posterior trunks. The anterior division is predominantly motor and gives rise to branches such as the masseteric nerve and the buccal nerve. In contrast, the posterior division is mainly sensory and includes the auriculotemporal, lingual, and inferior alveolar nerves, as well as the mylohyoid nerve. The inferior alveolar nerve, the largest branch of V3, further subdivides into several terminal branches. Its sensory components include branches supplying the mandibular molars and premolars, the incisive branch innervating the anterior teeth, and the mental nerve, which provides sensation to the chin, lower lip, and adjacent skin. The mylohyoid nerve represents the motor component, innervating the mylohyoid muscle and the anterior belly of the digastric muscle (2,4–6).

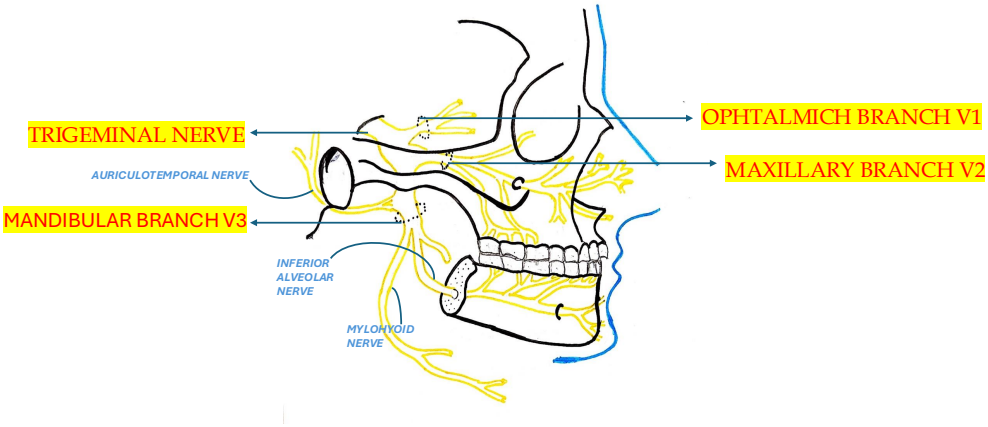


Figure 2: Trigeminal nerve: Ophthalmic, Maxillary and Mandibular branches, source: personal work

1.2. Overview of neurotropic viral infections

1.2.1. A deeper look into neurotropic viruses

A neurotropic virus is a virus that spreads through neural structures. These viruses can spread in the CNS (7). The recurrence and clinical presentation of these infections depend on several major factors, including viral genetics, host immunity, and environmental factors. Despite this, they are frequently misdiagnosed, often due to limited and superficial knowledge of the specific mechanisms of these viruses (8). Infections caused by neurotropic viruses often lead to poor prognosis and sometimes even death; they can cause irreversible damage, disturb the complex structural and functional organization of the central nervous system (9). The neurotropic viruses affect principally young children or the elderly (10). Those viruses can actually cause acute,

chronic, or latent infections (11). The further development of the disease depends mainly on the power of the viral load, the response of the immune host, and the ability of the virus to spread fast to immunoprivileged sites (9,11). Those different factors define the quickness and harshness of the future disease (9).

1.2.2. Viral entry and latency mechanisms

The neurotropic pathogens can enter the CNS. When a virus has this neuroinvasive property, it triggers the immune response; these immune episodes can be neuroprotective or cause large damage, and long-lasting, as seen in some neurodegenerative diseases (12). They can enter it by several routes, like retrograde axonal transport along motor and olfactory neurons, hematogenous dissemination across the blood–brain barrier, blood-cerebrospinal fluid barrier, meningeal-cerebrospinal fluid barrier, via direct infection of endothelial cells, or via spread of infected leukocytes across the blood-brain barrier into the brain parenchyma (9). The two identified specific locations of entry for neurotropic viruses are the blood-brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCSFB). Even though the virus first enters the blood-brain barrier and blood-cerebrospinal fluid barrier, the brain capillaries and choroid plexus are also important sites of entry in the CNS for bacteria, viruses, fungi, and parasites. The neurotropic viruses have several alternatives to be able to enter the CNS, transcellular, paracellular, and the « Trojan horse », depending on the virus. For example, herpes simplex virus 1 infects the host cells to pass the barrier (10). The viral proteins, to enter the CNS, play a role in tight junctions between brain microvascular endothelial cells (13). Once the neurotropic viruses have achieved entry into the CNS, there is an activation of microglia that act as defense; they are the brain-resident mononuclear phagocytes, representing about 10% of the total cell population of the brain (12). It is still primordial to analyze mechanisms of the entry of neurotropic viruses, leading to the many alterations and clinical manifestations that occur after the infection. Studies still need to be done on the different characteristics of neurotropic viruses entry (9).

The neurotropic viruses have the possibility to be latent and reactivated later; the latency is the retention of a viral genome within tissue devoid of detectable infectious virus, detectable viral proteins, or viral lytic transcript. Those viruses have established several techniques to evade the surveillance of the host's immunity, and can achieve entrance into the CNS (12). The virus is qualified as « dormant » when it is in the latent phase, but it has the capacity to reactivate at

any time (14). Suppose we take the varicella virus as an example of a neurotropic virus. In that case, its latent state is settled in human sensory neurons of ganglia on the neuraxis during primary infection and its disease (chickenpox) (15).

1.2.3 Viral reactivation

This latency can be stopped at any moment, and the host is re-infected again; this is called the reactivation, and it often occurs under stress (Figure 3). This stress led to a lytic infection. Those reactivation events lead to diseases such as herpes labialis, genital herpes, or herpes zoster, depending on the virus. It is a complex event dependent on viral and host factors. The latency and reactivation form a complex cooperation with the virus, neurons, and the immune system. The reactivation of latent infection is caused by triggers such as stress, the host's immunity, and neuronal activation. When the neurotropic viruses reactivate, they travel anterogradely on neuronal axons to the mucosal or skin surfaces, where they replicate and produce epithelial lesions (14).

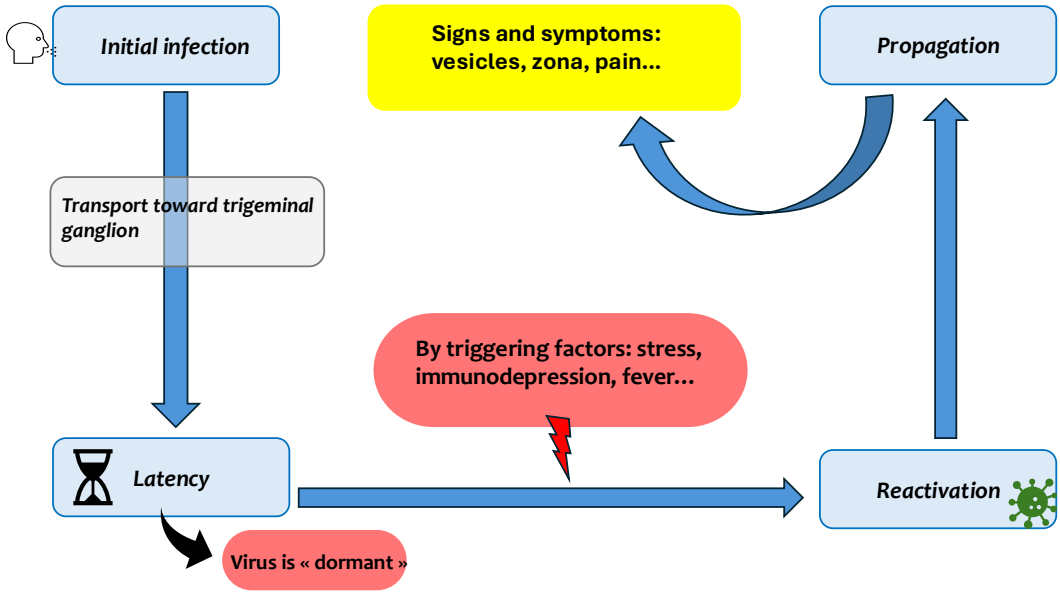


Figure 3: Summary of latency and reactivation process, source: personal work

1.3. Trigeminal viral infections

There are several different viral infections that can affect the trigeminal nerve. In this section, I will mainly focus on HSV-1, HSV-2, VZV, EBV, and CMV.

1.3.1. Clinical features of Herpes Simplex Virus Type 1 (HSV-1)

Herpes simplex viruses (HSV) are the most frequently identified viral pathogens in humans, and are also the most frequent cause of infectious encephalitis worldwide (8,9). HSV is characterized by a double-stranded DNA virus; being part of the Herpesviridae family, it is one of the most well-known neurotropic viruses, meaning it can enter through the central nervous system and infects surrounding like the peripheral nervous system (16,17). This virus initially affects the oral cavity, then the virus circulates along axons until it achieves the trigeminal ganglion, where it becomes latent until its reactivation. During this latency period, the virus stays inactive. The reactivation can happen or not, it can appear without any stimuli or be induced by some, resulting in different conditions, such as herpes labialis, encephalitis (90% of HSV encephalitis are due to HSV-1), facial palsy, or vestibular neuritis (9,16). Several risk factors may lead to reactivation more frequently: immunosuppression being one of the main factors, advanced age, diabetes mellitus, and malignancies (8,9,16,18). Antiviral treatment is beneficial to get rid of this herpes simplex virus; acyclovir is the first treatment for this virus, hugely decreasing the incidence of death. Before its use on patients, the mortality of herpes simplex patients with encephalitis was up to 70%, and several sequelae could be observed among people who survived (9,18,19). To detect the HSV correctly, the most commonly used tool is the molecular detection by polymerase chain reaction (PCR) (19).

HSV-1 primarily infects the orofacial region. The initial form presents as vesicles that are generally located on the skin of the face. These may appear as fluid-filled blisters, often painful but not malignant, which tend to recur at the same site as the primary infection. They are most commonly found at the mucocutaneous junction between the lips and the surrounding skin. This virus is transmitted through physical and sexual contact. Outbreaks often occur during periods of stress in the patient's life (20,21). During an episode of cold sores, the patient may experience pain, tingling, or even a burning sensation in the affected area, followed by the appearance of vesicles (Figure 4). Complete healing generally occurs within 7 to 10 days (22).

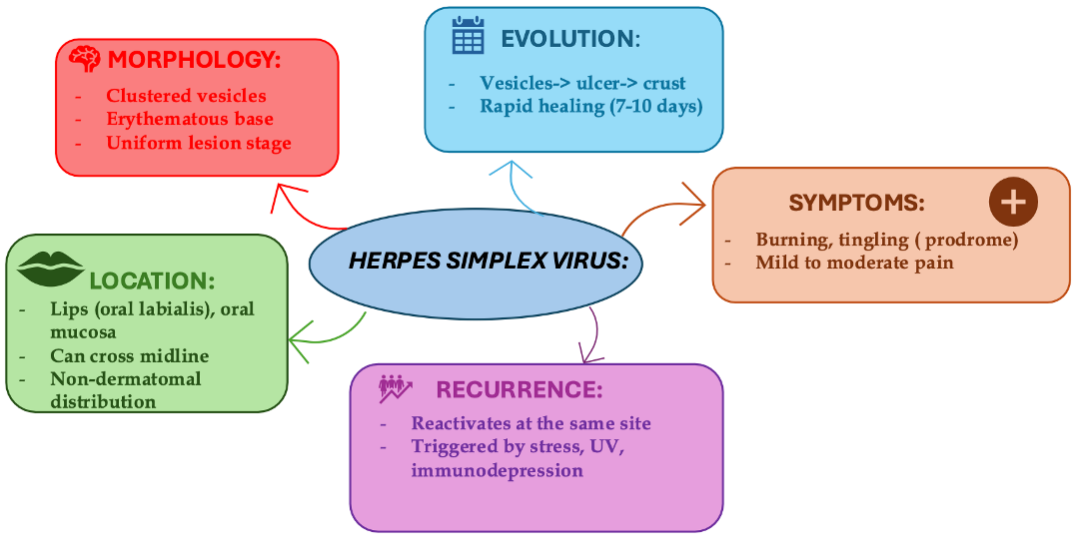


Figure 4: Clinical characteristics of HSV-1, source: personal work

1.3.2. Clinical features of Varicella-Zoster Virus (VZV)

The VZV, called varicella-zoster virus, is also from the family of human herpesvirus 3; its primary infection commonly appears in children. It is characterized by a double-stranded DNA virus, affecting only humans (8). For WHO, the varicella is one of the most contagious among eruptive disorders. Its principal transmission is aerial. This first infection is called varicella or chickenpox, resulting in fever and the presence of multiple vesicles at different periods, occurring 14-16 days after the first infection (9,23). We will diagnose this condition mainly clinically. This condition remains benign and rarely becomes complicated in children, but it can be complicated more easily in adults (23). When the varicella occurs, the virus goes into a latent phase in the spinal and cranial ganglia. The reactivation rarely occurs, but can occur, mostly in immunocompromised or elderly patients, and causes zoster (shingles). This virus is widely distributed around the world. People can be infected easily because it has a highly contagious system, transmitted mainly by cutaneous contact, or also airborne droplets (8). The pain that occurs during the varicella infection is very high; patients complain about a burning sensation on half of the face. Days after the first symptoms, vesicles appear on the area of burning. The patient can also present with an erythematous ulcer intraorally. After 10 days, appearances of pustules or even painful crusts can happen (24). Many complications can happen after herpes zoster; it is advisable to treat it rapidly or avoid it before it happens with the vaccine (25). The main one complication that can occur after zoster infection is the post-herpetic neuralgia (PHN), resulting in a persistent neuropathic pain, usually occurring on one side of the face, which occurs

after the resolution of shingles (Figure 5). This pain is often misdiagnosed and can easily be mistaken for dental pain, particularly in the maxillary and mandibular regions. It is therefore frequently misinterpreted, especially due to a lack of awareness and knowledge regarding post-herpetic neuralgia (9).

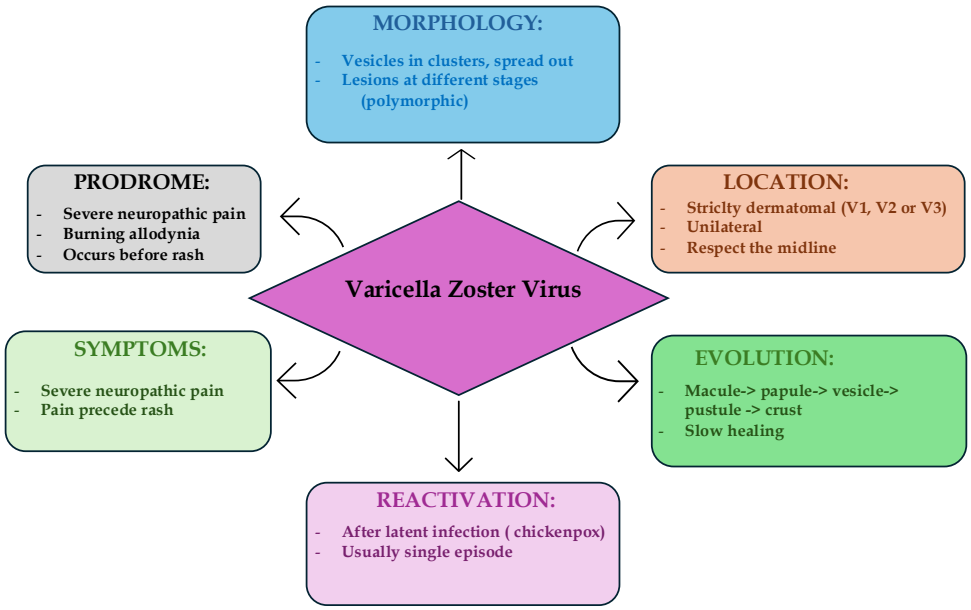


Figure 5: Clinical characteristics of Varicella-Zoster Virus, source: personal work

1.3.3. Other viruses affecting the trigeminal system (EBV, HSV-2, CMV)

EBV, called Epstein-Barr virus, was discovered by two scientists, Epstein and Barr. They discovered the virus particles in 1964 by testing an electron microscope on African Burkitt lymphoma cell. It is part of the human herpesvirus family (HHV-4). It is characterized by a double-stranded and linear DNA virus, also enveloped by a protein capsid. It has a worldwide distribution (Figure 6), its mode of transmission can be due to contact from secretions or infected equipment, or also by transfusion, and vertical transmission. The transmission happens mostly in an impoverished population, overpopulated, and mainly during infancy (8). EBV is highly prevalent, and its infection is actively associated with the pathogenesis of a variety of diseases like infectious mononucleosis, Burkitt lymphoma, and gastric cancer (26). Epstein-Barr virus is the cause of the development of infectious mononucleosis (IM), mainly affecting children or young adults. 4-6 weeks after the infection, clinical symptoms seem obvious: fever, inflammation of the pharynx, cervical lymphadenopathy, and hepatosplenomegaly (9,27).

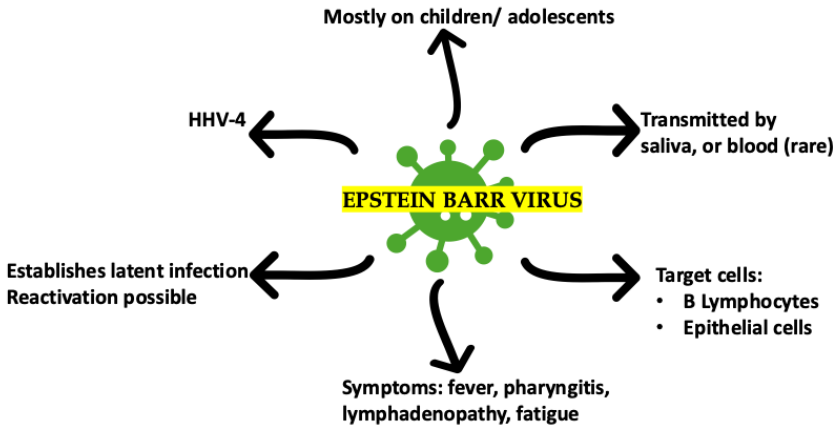


Figure 6: Epstein-Barr Virus Overview, source: personal work

The cytomegalovirus is also part of the herpesvirus family, represented by a linear DNA double-stranded virus. This virus spreads easily from direct contact, hospital-acquired, or by vertical transmission (Figure 7). There exist several risk factors for transmitting this virus, like poverty, sexual relations, or overpopulation (8). This particular virus has the capacity to cause several different diseases, from benign forms to life-threatening ones. The incubation period is between 3 to 12 weeks (9).

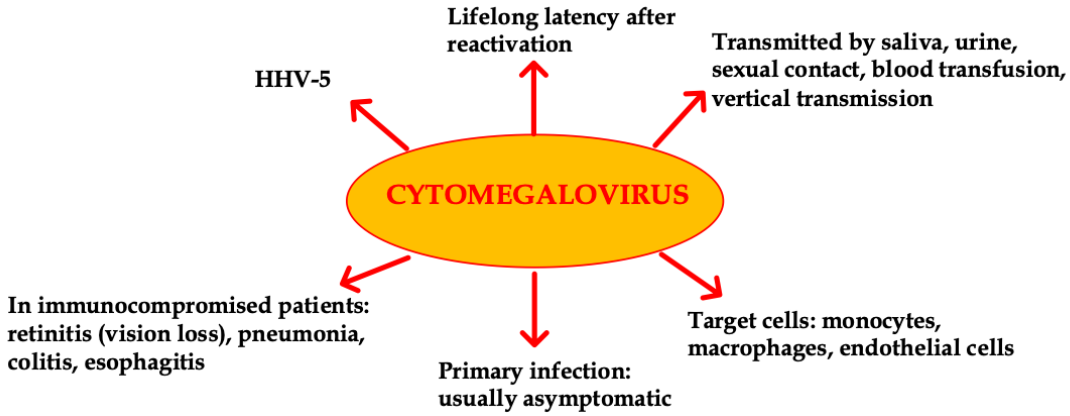


Figure 7: General characteristics of cytomegalovirus, source: personal work

Herpes simplex virus 2 is less prevalent than HSV-1, and infection is less frequent. This virus produces symptoms 3 to 7 days after the first infection in humans (9). Most of the alpha herpesviruses, including HSV-2, cause infections without symptoms and affect children more frequently (28). This virus primarily causes genital lesions, leading to the formation of vesicles in the genital area, buttocks, upper thighs, and perianal regions (Figure 8). These vesicles

subsequently evolve into ulcers. The primary infection may also present with fever, malaise, and localized lymphadenopathy. It is mainly transmitted through sexual contact. This infection persists over time and is characterized by periodic reactivation. It is highly prevalent; for example, approximately one in five adults infected (29).

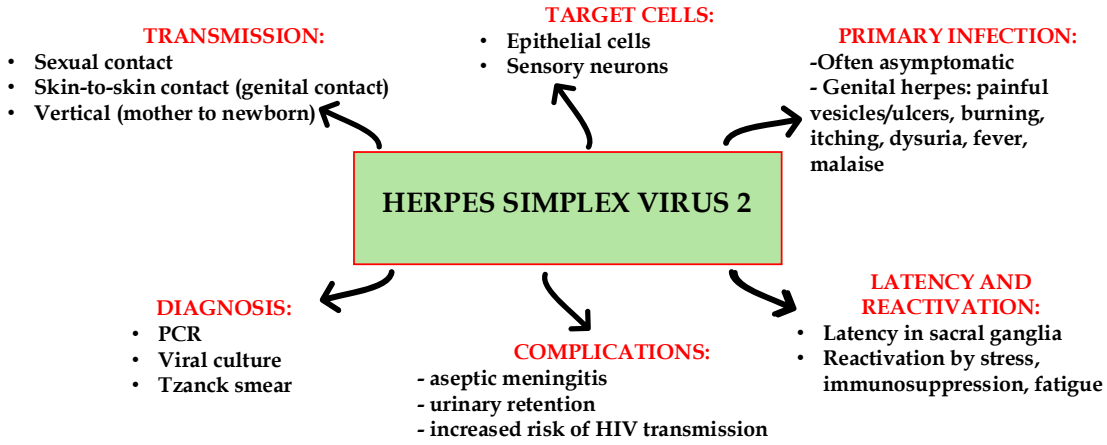


Figure 8: General characteristics of HSV-2, source: personal work

JUSTIFICATION:

PHN is the most common complication of herpes zoster. It is characterized by pain that persists for more than three months after the appearance of the vesicles. Some factors predispose individuals to develop this complication more easily, such as age, weakened immunity, and greater intensity of acute pain during VZV infection (30,31). Unfortunately, due to the weakened immune system of older individuals, PHN remains a condition that is difficult to fully cure. Patients often experience intense pain that can sometimes be unbearable (32). Treatment strategies are primarily focused on pain reduction, but some patients must continue medication for life because their condition does not resolve over time (31). Patients describe their pain as intense and intermittent, even in the absence of stimuli, and they frequently experience allodynia and hyperalgesia (33). Beyond severe pain, many other consequences have been reported; the impact of this condition extends to an overall reduction in quality of life and daily functioning (32). Although analgesics can temporarily reduce pain, long-term treatment remains uncertain due to the risk of liver and kidney damage from prolonged medication use. This is why alternative treatment options continue to be explored and developed over time (32). Overall, while treatments do exist, they remain uncertain and do not necessarily provide a permanent resolution for PHN.

It therefore seems essential to raise public awareness about the risk of this complication, particularly among high-risk groups, and to improve education on prevention. The existence of the vaccine is still not widely known. The vaccine, which targets VZV, is called Zostavax. The most effective way to prevent PHN is to avoid the initial VZV infection, and thus to receive this vaccine. Although the vaccine has proven its effectiveness, it remains underused, partly due to its cost (31). People over the age of 50 should be informed about and consider this vaccine, as they are at higher risk of infection. They should also receive early treatment and more careful follow-up compared to individuals without risk factors (30).

2. OBJECTIVE

The objective is to explore the possible treatments used in managing postherpetic neuralgia as a potential complication.

3. MATERIAL AND METHODS

For this literature review, a broad and rigorous search of the existing literature was conducted, including the CRAI Dulce Chacon library that offers multiple articles and books, in addition to several trusted databases like PubMed and Scopus. To analyze different articles relevant to the subject, the following keywords were used: trigeminal nerve, trigeminal viral infections, herpes zoster virus, post-herpetic neuralgia, reactivation of varicella, trigeminal ganglion, varicella zoster virus latency, trigeminal ganglion virology, neurotropic viruses, trigeminal neuralgia viral etiology, herpesvirus latency. On December 4th 2025, the advanced research questions used in the databases was: ("post-herpetic neuralgia") AND ("treatment") OR ("post-herpetic neuralgia") AND ("drugs") OR ("post-herpetic neuralgia") AND ("gabapentin") OR ("post-herpetic neuralgia") AND ("lidocaine") OR ("post-herpetic neuralgia") AND ("tricyclic anti depressants") OR ("post-herpetic neuralgia") AND ("pregabalin"). Then a selection from these 2283 articles was made, adding filters such as «articles of the last 10 years» and « free full text », and found 1171 articles. A meticulous selection of articles based on specific inclusion and exclusion criteria was made:

EXCLUSION CRITERIA	**INCLUSION CRITERIA**
Scientific articles published before 2015	Scientific articles published after 2015
Scientific articles from low-quality sources	Scientific articles from PubMed, Scopus
Information not relevant to trigeminal viral infection	Information relevant to trigeminal infection
Articles not fully available	Articles available in free-full text
Articles written in other languages	Articles written in English, French or Spanish

Table 1: Inclusion and exclusion criteria

The PICO question (= participants, intervention, comparison and outcomes) chosen for this literature review can be stated as:

- **Participants:** in patients with post-herpetic neuralgia **(P)**,
- **Intervention:** receiving a pharmacological treatment (gabapentin) **(I)**,
- **Comparison:** compared to an alternative management strategy **(C)**,
- **Outcome:** aims to reduce the signs and symptoms of patients affected by this condition **(O).**

Defining the PICO question clarified the research objective, enabling a more thorough analysis of the selected articles and facilitating a deeper understanding of the topic.

4. RESULTS

63 articles were obtained from PubMed and 2220 from Scopus for the primary search. Among them, 42 became possible articles via screening by titles and abstracts. Some of this articles were excluded because of being older than 10 years, not available in full text, or not written in English. Finally, a total of 10 articles were chosen to be included in this review.

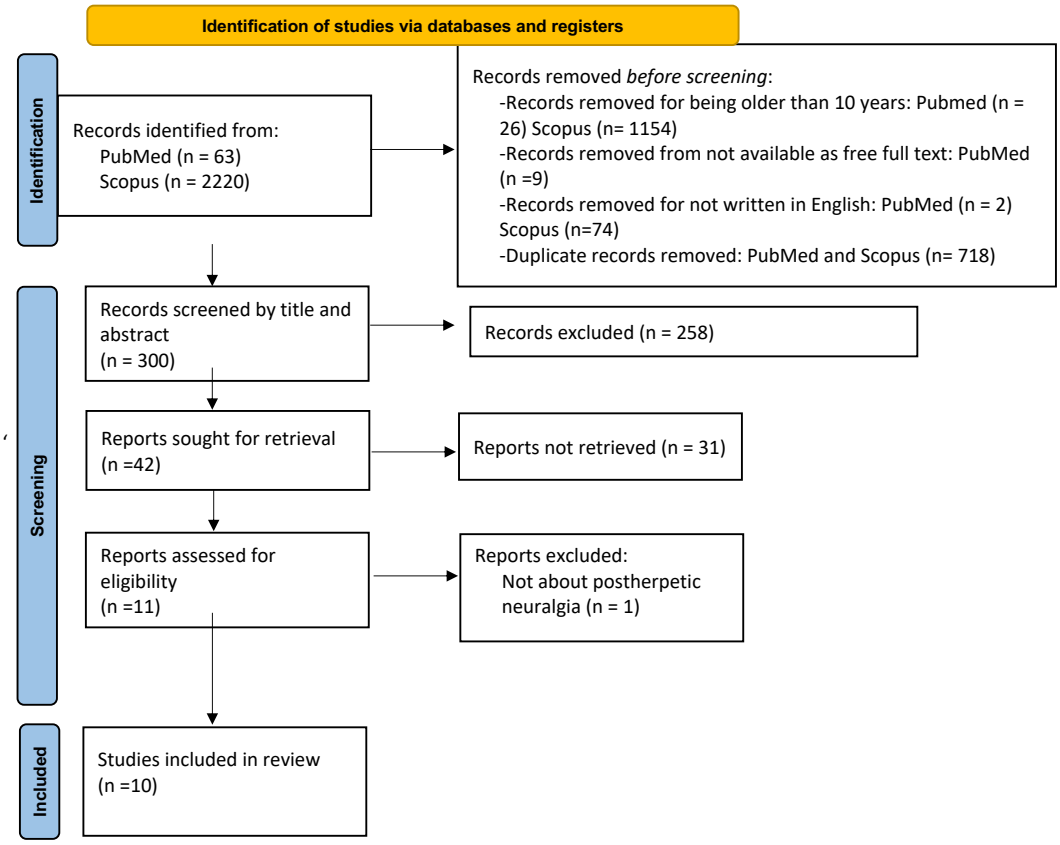


Figure 6: Prisma flow chart of the included studies in this review (34).

10 studies have been selected to compare different types of treatment for PHN. In the next table, there is a summary of all of them (Table 3).

	Year and authors	Country	Type of study	Sample size	Age range	Objective	Summary of the study	Outcomes
1	2022, Sameh Abdelhalik Ahmed et al. (35)	Egypt	Randomized controlled trial	75 participants	Not specified.	Evaluate the efficacy of ESPB on patients suffering from postherpetic neuralgia, and magnesium sulphate effects, comparing three groups.	Compare 3 groups: -Group A: sham ESPB (2ml normal saline) -Group B: ESPB with 20ml of bupivacaine -Group C: ESPB with 20ml of bupivacaine and magnesium sulphate.	ESPB shows real efficacy, decreasing in pain score and analgesics need. Magnesium sulphate provides no additional benefit to patients; outcomes are similar with or without it.
2	2025, Yue Wang et al. (36)	China	Randomized controlled trial	220 participants	Not specified	Evaluate pain relief, efficacy of the treatment, tolerability, and adverse effects, including sleep quality between Duloxetine and Amitriptyline.	Compare 2 groups randomly assigned: -Group 1: duloxetine with pregabalin -Group 2: amitriptyline with pregabalin.	Between the 2 different groups, an improvement in pain has been significant, but there is not major difference between the two, only amitriptyline with pregabalin shows more dry mouth cases than duloxetine.

3	2022, Esraa H. Abdelwahab et al. (37)	Egypt	Randomized controlled trial	90 participants	Over 50 years old	Study efficiency and safety of single-injection thoracic paravertebral block (PVB) and erector spinae plane block (ESB)in patients with acute thoracic herpes zoster for the prevention of postherpertic neuralgia. The aim is to evaluate which one works better.	Compare 3 groups: Group A: ESB received US-guided ESB with bupivacaine 0.5%, + dexamethasone Group B: PVB received US-guided PVB with bupivacaine 0.5%, + dexamethasone Group C: control group.	The study found that both techniques were effective for pain relief, but it showed that the ESB technique is safer, as side effect such as hypotension was not reported.
4	2022, Lei Sheng et al. (38)	China	Randomized controlled trial	70 participants	Elderly patients	Evaluate the efficacy and safety of pulsed radiofrequency (PRF), and short-term spinal cord stimulation (stSCS) in patients suffering from postherpetic neuralgia.	Compare 2 groups (equally randomized): Group 1: patients treated with pulsed radiofrequency Group 2: patients treated with short-term spinal cord stimulation.	The study found that both treatments were effective in reducing pain in patients with postherpetic neuralgia. However, stSCS had a superior analgesic effect compared to PRF, was associated with a better quality of life, and required lower doses of pregabalin.

5	2022, Kyung Ah Han et al. (39)	South Korea	Clinical trial and Randomized Controlled Trial	371 participants	Not specified.	Study efficacy of once-daily SR pregabalin or twice-daily IR pregabalin over diabetic peripheral neuropathy or postherpetic neuralgia for 12 weeks.	Compare new once-daily SR pregabalin formulation with twice-daily IR pregabalin, his efficacy in reducing pain and tolerability.	The two treatments are equivalent: the new once-daily SR pregabalin has similar effects to twice-daily IR pregabalin, and both are well tolerated.
6	2022, Cheng-Fu Wan et al. (40)	China	Randomized Controlled Trial	120 participants	Elderly patients	Study safety and efficacy of pulsed radiofrequency (PRF) neuromodulation at 2 different frequencies on gasserian ganglion, in the prevention of PHN after herpes zoster.	Compare 2 groups: Group 1: patients receive a single cycle of high-voltage, long-duration PRF Group 2: patients receive three cycles of standard PRF.	Both PRF modes were effective in reducing pain and preventing postherpetic neuralgia; however, the high-intensity PRF mode (group 1) appeared to provide better efficacy while remaining safe and well tolerated this population.
7	2017, Dong Wang et al. (41)	China	Randomized clinical trial	40 patients	Not specified	Study the efficacy and safety of pulsed radiofrequency (PRF) + pharmacological therapy in patients suffering from postherpetic neuralgia (PHN).	Compare 2 groups: Group 1: patients are treated with PRF + pharmacological treatment Group 2: patients are only treated with pharmacological treatment (control group).	The study indicates better results for Group 1, with patients treated with PRF, experiencing better pain relief and good tolerability.

8	2017, Stephan A Schug et al. (42)	USA and Australia	Randomized controlled trial	747 participants	Not specified	Study how the use of concomitant medications influences the effectiveness and tolerability of pregabalin in treating neuropathic pain.	Compare 2 groups: Group 1: patients treated with concomitant neuropathic pain medications Group 2: patients not treated with concomitant neuropathic pain medications.	The study indicates that the efficacy of pregabalin and the incidence of adverse events in patients with neuropathic pain are largely unaffected by the concomitant use of other neuropathic pain medications.
9	2022, Shumao Zheng et al. (43)	China	Randomized clinical trial	40 participants	Not specified	Study effects of pregabalin in patients suffering from postherpetic neuralgia by functional magnetic resonance imaging (fMRI)	Compare 2 groups: Group 1: treatment group Group 2: control group	The study indicate that Pregabalin effectively relieved pain in patients with postherpetic neuralgia. Analysis of resting-state fMRI using deep learning showed changes in brain activity linked to pain, helping to explain how pregabalin works. The treatment was also found to be safe and well tolerated.

10	2025, Tao L. et al. (44)	China	Randomized Clinical trial	134 participants	Not specified.	Study the efficacy of gabapentin + pregabalin compared to gabapentin alone, in the treatment of postherpetic neuralgia, by analyzing patient-reported outcomes and inflammatory cytokine reduction.	Compare 2 groups: Group 1: patients treated with gabapentin alone (GB) Group 2: patients treated with gabapentin and pregabalin (GBP) Orally for 8 weeks.	The study concluded that gabapentin combined with low-dose pregabalin may be effective in alleviating pain and decreasing inflammatory factors.

Table 3. Table summarizing the 10 studies selected to compare different treatment options for postherpetic neuralgia

5. DISCUSSION

The studies included in this review evaluated different therapeutic strategies for postherpetic neuralgia, including pharmacological optimization, interventional procedures, and combined approaches. Among the selected studies, some described treatment approaches for postherpetic neuralgia that were not specifically limited to the trigeminal region. These studies were nevertheless included as they were considered relevant and provided valuable insights into therapeutic strategies, thereby contributing to a more comprehensive understanding of postherpetic neuralgia management and supporting the overall conclusions of this work.

5.1. Drug-based treatments

5.1.1. Gabapentinoids alone and in combination

Postherpetic neuralgia is one of the most challenging complications to manage, as the associated pain can be severe and difficult to relieve. This type of neuropathic pain represents a significant therapeutic challenge. Gabapentinoids, are anticonvulsants drugs, and are considered first-line treatments to treat any neuropathic pain. Clinicians widely recommend them to help alleviate this type of pain by reducing neurotransmitter release via calcium channels binding. The article published by Zheng *et al.* 2022, demonstrates that pregabalin acts on two levels. Neuroimaging allows us to understand where and how pain reduction occurs. Beyond its action on peripheral calcium channels, pregabalin also affects the brain. In addition to clinical improvement and significant reductions in neuropathic pain scores, this study provides a more objective perspective through medical imaging. It shows that pregabalin reduces hyperactivity in certain brain regions associated with pain perception (43).

Several of the selected studies examined several different drugs, different doses, combinations of treatments, and their side effects on participants. The studies included in the results part are heterogeneous, some describing monotherapy with pregabalin alone, others analyzing combined drug treatment. This enables us to effectively identify all possible treatment options for postherpetic neuralgia by analyzing the primary medication (pregabalin) both on its own and in combination, to achieve optimal results (36,39,42–44). The response to gabapentinoids alone is often insufficient to relieve the pain experienced by patients suffering from postherpetic neuralgia, and this explains why we find many articles presenting combination treatments that include gabapentinoids (36,42–44). The study by Wang *et al.* 2025, also shows that pregabalin

is rarely used alone in moderate to severe forms of PHN, as patients treated with pregabalin often continue to experience significant pain and poor sleep quality during the initial phases of treatment. Combining this therapy with duloxetine or amitriptyline, in this case, improves pain outcomes in patients suffering from PHN. Gabapentinoid treatments combined with duloxetine and amitriptyline have overall been shown to improve pain in patients without generally increasing adverse effects (36). This is consistent with Shug *et al.* 2017, analyses, which show that the response to pregabalin is positively influenced by concomitant treatments as well as the overall medication burden, demonstrating that therapeutic efficacy is greater within a comprehensive treatment approach rather than with pregabalin prescribed alone (42).

Gabapentinoids remain the initial treatment of choice, and several formulations are available. Han et al. demonstrated in their study that the extended-release formulation of pregabalin is as effective for pain relief as the immediate-release formulation. Moreover, it offers the advantages of fewer side effects, better overall tolerability, and potentially improved adherence (39).

Among the gabapentinoids, several medications are available, including pregabalin and gabapentin. Lu Tao *et al.* 2025, therefore, investigated which of these was proven to be more effective in patients suffering from postherpetic neuralgia. Their study established that the combination of pregabalin and gabapentin provided greater benefit than either medication used alone. Together, these medications demonstrate a greater reduction in pain than when used individually, along with improvements in sleep and overall quality of life, without a significant increase in adverse effects. Despite having similar mechanisms of action, pregabalin and gabapentin may exhibit pharmacodynamic synergy when used together (44).

To analyze drug tolerability and the associated adverse effects, these different studies mainly demonstrate that side effects are dose-dependent. The most commonly reported include drowsiness, impaired sleep quality, and dizziness, while cognitive disturbances may also occur (36,39). Nevertheless, the studies suggest that long-term combination regimens using lower doses may provide a better balance between efficacy and tolerability (36,39,44).

Overall, the data agree that pregabalin is recommended as first-line therapy. The efficacy and rapid onset of action of this medication have been primarily demonstrated through various assessments, including neuropathic pain scoring systems (44). It is nevertheless very interesting to combine this treatment with duloxetine or amitriptyline; in both cases,

patients' pain levels are significantly lower than with pregabalin alone. These medications have different mechanisms of action and therefore work in combination to achieve maximum efficacy. Pregabalin acts on voltage-gated calcium channels, reducing the release of excitatory neurotransmitters. Duloxetine and amitriptyline, on the other hand, inhibit the reuptake of serotonin and norepinephrine, thereby strengthening the descending inhibitory pain pathways. As a result, pain is "blocked" at two different levels of the nervous system. This represents a multimodal, multi-mechanistic approach to pain management. By combining these two treatments, pain is managed more effectively without increasing the pregabalin dose, thereby limiting potential toxicity and side effects (36). The efficacy and pain response to pregabalin also depend on the analgesic treatments the patient is receiving simultaneously, as well as their overall medication burden. Shug et al. notes that other medications taken at the same time can influence the effectiveness of the first-line treatment. Opioids, antidepressants, or other drugs may have additive or opposing effects on the chosen therapy. Side effects can also be amplified, for example, the combination of opioids and pregabalin increases the likelihood of drowsiness, which can significantly impact tolerability. Patients suffering from PHN are often elderly and likely on multiple medications, making it difficult to predict all potential drug interactions (42).

Overall, gabapentinoids are the first chosen treatment, essential for managing neuropathic pain. However, all these studies primarily suggest using them in combination, as this is where maximum efficacy is achieved. Their effectiveness is optimized through mechanistically complementary associations, consideration of the patient's overall medication context, formulation optimization, and, in some cases, combining drugs from the same class. Each patient is a specific case and must be managed individually, taking into account factors such as medication context, pain stage, and potential side effects (36,39,42,44).

5.2. Interventional approaches

5.2.1. Nerve blocks

Some of the nerve blocks described in this work are primarily applicable to thoracic or dorsal postherpetic neuralgia; however, they support the concept that pharmacological treatment alone may be insufficient and that combining it with interventional approaches can improve pain management. In parallel, nerve blocks targeting the branches of the trigeminal nerve have also been shown to be effective. Although applied in different anatomical regions, these techniques rely on similar principles of targeted neural modulation, allowing a conceptual link to be established between trigeminal nerve blocks and thoracic approaches such as the erector spinae

plane block or the thoracic paravertebral block. Furthermore, beyond their role as part of a multimodal strategy combined with pharmacological treatment, these techniques may also contribute to the prevention of postherpetic neuralgia.

In the article by Abdelwahab *et al.* 2022, different techniques are analyzed, including the ultrasound-guided Erector Spinae Plane (ESP) block and the ultrasound-guided Thoracic Paravertebral Block (TPVB). The objective is to relieve acute thoracic shingles pain and to prevent its progression to PHN. Both blocks have been shown to be effective in reducing patient pain. TPVB is slightly more effective in the short term but involves a more complex technique, whereas the ESP block is less invasive and therefore easier to perform. These techniques provide early pain relief and may act as protective factors against the development of PHN. They can be used as complementary treatments alongside gabapentinoids due to their segmental, system-level analgesic effects. In the same way, trigeminal nerve blocks offer a locally targeted approach that is mechanistically complementary to systemic gabapentinoid therapy, leading to a more comprehensive multimodal analgesic strategy. Furthermore, these regional block techniques remain underused and insufficiently discussed in the management of postherpetic neuralgia. In particular, trigeminal nerve blocks for postherpetic neuralgia affecting the V2 and V3 branches of the trigeminal nerve may be increasingly considered as part of a multimodal approach (37).

5.2.2. Neuromodulation

Sheng *et al.* 2022, compare in his article continuous spinal cord stimulation (SCS) with pulsed radiofrequency (PRF), a localized, non-lesional stimulation, in elderly patients suffering from PHN. They demonstrate that both techniques result in significant reductions in pain scores, providing considerable relief for patients. SCS produces faster and longer-lasting effects, while PRF is less invasive, though its effects are shorter in duration. These treatments can be used for patients whose pain is not adequately controlled by conventional methods. PRF is particularly useful for preventing pain or managing so-called “moderate” pain (38). Wan et Song *et al.* 2022, compared two different PRF modalities for the prevention of PHN in elderly patients affected by acute or subacute trigeminal herpes zoster. Their study demonstrated that PRF reduces the risk of postherpetic neuralgia, and that the optimized pulsed mode provides excellent pain relief and highly effective prevention. It is a minimally invasive technique with very good tolerability. However, PRF is also used for prevention for PHN, as it may be insufficient against established neuropathic pain. It is therefore recommended to use it as a complement to pharmacological treatment (40).

These studies do not discuss using these treatments as a monotherapy for PHN; as we will see in the next section, a complementary approach is always necessary for managing neuropathic pain (37,38,40).

5.3. Combined strategies

5.3.1. Nerve blocks and pharmacological adjuvants

In the study by Ahmed *et al.* 2022*,* the efficacy of combining an erector spinae plane (ESP) block with magnesium was evaluated for pain reduction in patients with PHN. The authors specifically assessed the added value of magnesium to this technique, and the results showed that this combination achieved greater pain reduction compared to the ESP block alone. Magnesium helps reduce central sensitization by acting as an NMDA receptor antagonist, while the nerve block provides peripheral modulation. This complementary mechanism is beneficial for the patient. Combining treatments that act at different levels of the pain pathway greatly enhances pain reduction and consequently reduces the need for analgesics, including opioids, to relieve the patient. Although efficacy was demonstrated in non-trigeminal postherpetic neuralgia, the results still suggest that combined treatment is superior to either approach alone, a conclusion likely applicable to trigeminal involvement due to shared neuropathic mechanisms (35).

5.3.2. PRF and drug-based treatments:

In this section, a combination therapy was also studied, but this time Wang *et al. 2017,* evaluated pulsed radiofrequency (PRF) combined with standard pharmacological treatment for PHN. The results showed that PRF plus medication led to a greater and longer-lasting reduction in pain scores, decreased analgesic requirements, and promising objective and subjective outcomes, including patient-reported improvement. As in other studies, this combination proved effective because the two interventions act through different mechanisms: local neuromodulation and systemic pharmacological action, pulsed radiofrequency acts locally on the trigeminal nerve, thereby exerting a peripheral effect, whereas pharmacological treatments act on central sensitization by reducing overall neuronal excitability. To conclude, combination drug-based strategies in the treatment of PHN consistently demonstrate a better pain response (41). Overall, this multimodal strategy appears to be one of the most effective approaches for patients suffering from postherpetic neuralgia (PHN).

5.4. Overall comparison

5.4.1. Efficacy

Overall, across all these articles, gabapentinoids remain the therapeutic cornerstone for treating patients with PHN. However, the studies converge on the same point: combination therapies are often the most effective. The combination of duloxetine with pregabalin shows excellent efficacy for pain reduction and improvement in quality of life, with a synergistic effect between serotonergic/noradrenergic modulation and calcium channel inhibition (36). The combination of gabapentin and pregabalin is also frequently used and leads to greater pain reduction than pregabalin alone (44). To maximize treatment effectiveness, combining medications with gabapentinoids is essential (36,42,44,45). To study the most effective treatments in patients, the subjective component is assessed through patient-reported outcomes, such as their perception of pain, sleep quality, and overall well-being. In addition, functional MRI (fMRI) combined with deep learning helps demonstrate changes in brain functional networks under pregabalin treatment, thereby validating its action on central sensitization (43). Despite these treatment optimizations and therapeutic combinations, complete relief of neuropathic pain remains very difficult to achieve. The occurrence of side effects is not uncommon and can sometimes limit access to full treatment. In such cases, the combination with nerve blocks and neuromodulation becomes particularly important (36,39,44). Unlike pharmacological treatments, which mainly target the central mechanisms of pain, nerve blocks act on peripheral nociceptive transmission. Nerve blocks have demonstrated effectiveness in reducing pain, with overall comparable analgesic effects, as both are effective and provide rapid relief (37).

The same applies to neuromodulation. Pulsed radiofrequency (PRF) has been shown to reduce the incidence of PHN in elderly patients, and its combination with pharmacological treatment appears to be even more effective (38,40,41).

Pharmacological treatments and nerve blocks should therefore be viewed as complementary rather than competing strategies. Current evidence generally supports the use of nerve blocks in earlier or acute phases of treatment, while pharmacological therapies are more suited for long-term pain control. In conclusion, the management of postherpetic neuralgia likely requires a multimodal strategy targeting both peripheral nociceptive transmission and central sensitization mechanisms (23,24,27,31).

5.4.2. Safety and tolerability

Considering the safety and tolerability of medications is a crucial aspect in the treatment and management of patients suffering from PHN, particularly in elderly individuals, who represent the majority of cases and are often polymedicated. It is therefore important to be aware of potential drug interactions to avoid adverse effects.

In general terms, gabapentinoids remain effective medications that are well tolerated by the majority of patients (39,42,43). Gabapentinoids are associated with frequent side effects, most of which are well-known: dizziness, drowsiness, fatigue, and balance disturbances. These effects are generally dose-dependent and can therefore often be easily avoided (36,39,39,42,44). A study has also shown that there are different methods to improve overall tolerability and minimize side effects as much as possible; pregabalin SR demonstrated better overall tolerability, with more stable plasma levels (39). Combination therapy with gabapentin and pregabalin has shown greater efficacy than monotherapy; however, it is not without drawbacks, as this combination increases adverse effects, thereby limiting tolerability (44). But once again, it depends on the individual case. Indeed, the combination of duloxetine and pregabalin has shown better tolerability, with fewer anticholinergic effects, whereas the combination of amitriptyline and pregabalin is associated with more side effects, such as dry mouth, sedation, and orthostatic hypotension. Tolerability fully depends on the specific drug combinations used (36).

On the contrary, to counter these various side effects experienced by patients during treatment, new approaches have emerged: interventional techniques. Pulsed Radiofrequency (PRF), for example, has shown promising results: it is minimally invasive, has excellent tolerability, and most importantly, no systemic side effects. The few reported risks are localized pain or nerve injury (rare cases). Compared to medications, it offers a better systemic safety profile (36,38,41). Similar results are observed with SCS, ESP, and PVB, all interventional techniques that provide long-term efficacy and acceptable tolerability, with limited systemic adverse effects (35,37,38). Some studies combining both approaches, pharmacological therapy and interventional techniques, also show excellent results, with improved tolerability for patients. Overall, the best tolerability is observed with interventional techniques, as they present little to no side effects (41).

5.4.3. Recommendations depending on patients

Neuropathic pain remains extremely severe, presenting a challenging treatment issue. Physicians must manage pain so that it remains bearable while minimizing the side effects of the various treatments. Each patient is a unique case, depending on the nature of their pain, current medications, and personal preferences. Older adults are the most frequent patients undergoing these treatment procedures. Gabapentin monotherapy is not recommended for this population due to its numerous side effects. Instead, it is advised to combine gabapentinoids with interventional techniques such as PRF in refractory cases (38,40).

In the most severe cases, where patients may resort to opioids due to unbearable pain, or in refractory cases, it is strongly recommended to use combination therapies, employing both pharmacological treatments as well as interventional techniques such as PRF. Better efficacy is achieved by combining these techniques than with monotherapy (35,36,38,40,41).

It has been shown that patients with comorbidities achieve better treatment outcomes with the combination of duloxetine and pregabalin. This is the recommended approach, while these patients should avoid amitriptyline, particularly due to its anticholinergic effects (36).

For patients with early PHN or even acute herpes zoster, early intervention with PRF and nerve blocks is necessary. This approach may even prevent the progression of PHN before it becomes a significant concern for the patient (35,40).

For patients most sensitive to side effects, whose primary goal is to eliminate pain without experiencing negative effects, the best options are PRF and nerve blocks, as they minimize side effects (38,38,40,41,46).

If the patient is concerned with minimizing cost, it is true that some interventional techniques can indeed be more expensive. In such cases, the clinician may consider for treatment with gabapentinoids (38).

Treatment selection must be carefully personalized by the clinician based on the patient's age, pain severity, comorbidities, medication tolerability, and accessibility. All these criteria highlight the importance of individualized treatment strategies. In conclusion, there is a clear shift toward combining interventional approaches with the usual gabapentinoid therapy rather than relying on gabapentinoids alone (35,37,37,38,40–42).

6. CONCLUSIONS

1. Viral infections of the trigeminal nerve have a significant impact and can lead to various complications. Here, we have particularly studied the complication resulting from varicella-zoster, the postherpetic neuralgia. Postherpetic neuralgia (PHN) is a persistent neuropathic pain lasting more than three months after the onset of a rash, more commonly affecting older adults and immunocompromised individuals. Involvement of the trigeminal nerve can have serious consequences due to its anatomical location, depending on the branch affected. This may lead to nerve damage as well as peripheral and central sensitization. Beyond affecting the facial region, PHN significantly impacts quality of life, including sleep, mood, and overall psychological health, often contributing to anxiety and depression. This infection, which occurs after a period of latency in the trigeminal ganglion, is highly important because it involves facial pain and complications that may persist over time, greatly affecting the patient's life. Treatment remains complex when it comes to providing long-term relief for the patient. Postherpetic neuralgia remains one of the most debilitating complications of herpes zoster affecting the trigeminal nerve.

2. From the various studies, it is evident that the optimal treatment strategy for patients suffering from postherpetic neuralgia (PHN) has evolved over time, shifting from single-drug approaches to multimodal strategies. These multimodal strategies include both pharmacological treatments and interventional therapies. The aim of this new approach is, of course, to reduce pain while also improving quality of life, minimizing known adverse effects as much as possible. It provides a more personalized and targeted approach for each patient, taking into account their individual needs and priorities.

3. The proper management and treatment of postherpetic neuralgia (PHN) remain a challenge. The persistence and variability of cases make it difficult to completely eliminate the pain. Other factors, such as variability in patients' responses to treatment, side effects, and tolerance, as well as sometimes delayed diagnosis and more complex cases in older populations, contribute to differences in treatment effectiveness, making each case unique.

4. This is why it is essential to understand the importance of this complication, to detect it early, and to intervene as quickly as possible once diagnosed. Above all, prevention is crucial in order to raise awareness among those most at risk. To achieve this, early antiviral therapy during acute herpes zoster is necessary, especially for high-risk patients. The role of vaccination (zoster vaccines) is also key, particularly for older individuals and those most susceptible to being affected. In addition, prompt treatment at the time of PHN diagnosis is essential. As with many diseases, prevention remains the most effective strategy—often even more so than treatment itself.

5. In conclusion, post-herpetic neuralgia of trigeminal origin remains a complex and challenging condition, requiring early intervention, individualized management, and continued research efforts to improve patient outcomes and quality of life. Despite advances in therapeutic strategies, significant limitations persist, particularly in achieving complete and sustained pain relief. Future progress will depend on a better understanding of underlying mechanisms and the development of more targeted and effective treatments.

7. SUSTAINABILITY

The importance of sustainability in the medical field lies in its ability to promote long-term progress through responsible therapeutic and pharmacological approaches designed to remain effective over time. In the context of this literature review, focused on trigeminal nerve infections and the treatment and management of post-herpetic neuralgia (PHN), sustainability refers to the development of diagnostic and therapeutic strategies that are both effective and durable. It therefore encompasses social, economic and environmental dimensions.

Socially, raising awareness about the viral mechanisms underlying PHN is essential for earlier diagnosis and more effective treatment. It is particularly important to educate individuals over 60 years old and immunocompromised individuals (at-risk individuals) about doing regular check-ups, examinations, and considering vaccination against herpes zoster (VZV/ Shingrix) to reduce the incidence of post-zoster complications. Increased awareness in older populations would facilitate earlier detection by recognizing prodromal symptoms and initiating treatment at the appropriate time.

From an economic perspective, improving the detection of herpes zoster in its prodromal stage and ensuring fast and effective treatment can significantly reduce healthcare costs. Limiting complications such as PHN decreases the long-term use of analgesics, chronic pain, and repeated consultations with various medical specialists. Indirectly, these measures contribute to an overall reduction in the medical resources required.

From an environmental perspective, by preventing the complication of PHN with the herpes zoster vaccine, we prevent the disease itself, thereby reducing the overall environmental footprint. Non-pharmaceutical approaches, such as interventional neuromodulation strategies, represent innovative and more sustainable solutions.

Establishing strategies that prevent these complications would lead to enhanced quality of life, reduced pain in affected patients, and a faster reintegration into social and professional life.

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9. ANNEXES