

Effectiveness of lidocaine patches in the treatment of post-herpetic neuralgia on the face: a systematic review and meta-analysis

Efetividade dos emplastos de lidocaína no tratamento na nevralgia pós-herpética em face: revisão sistemática e meta-análise

Efectividad de los parches de lidocaína em el tratamiento de la neuralgia posherpética em la cara: revisión sistemática y metanálises

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Abstract

The post-herpetic neuralgia (PHN) is one of the most challenging neuropathies to resolve. There are many treatment options with varying degrees of effectiveness. This paper conducts a systematic review of the literature on lidocaine patches in the treatment of these neuralgia. A systematic review according to the PRISMA guidelines on lidocaine patches in the treatment of postherpetic neuralgia. The PROPERO registration has been carried out. A meta-analysis was performed with RevMan 5.3. Nine articles were included according to criteria. A table of excluded articles and their reason was carried out. Lidocaine patches are effective in treating post-herpetic neuralgia and are safer than other treatments, making them available for elderly patients with co-morbid conditions when other treatments cannot be used due to side effects. Lidocaine patches should be considered the first line therapy in the treatment of post-herpetic neuralgia of the face because of their safety and cost-benefit ratio.

Keywords: Anesthetics; Lidocaine; Herpes Zoster; Neuralgia.

Resumo

A nevralgia pós-herpética é uma das neuropatias mais desafiadoras. Há muitas opções de tratamento com variados graus de efetividade. O presente trabalho realizou uma revisão sistemática sobre o uso dos emplastos de lidocaína no tratamento desta nevralgia. Foi realizada uma revisão sistemática seguindo o protocolo PRISMA sobre os emplastos de lidocaína no tratamento da nevralgia pós-herpética. Foi realizado o registro do protocolo no sistema PROSPERO. A meta-análise foi criada por meio do software RevMan. Nove artigos foram incluídos de acordo com os critérios de inclusão e exclusão. Uma tabela dos artigos incluídos e a razão da exclusão foi criada. Os emplastos de lidocaína são efetivos no tratamento da nevralgia pós-herpética e são mais seguros do que outras medicações, o que os torna úteis em pacientes idosos com comorbidades, onde a utilização de outras medicações gera uma série de efeitos adversos. Os emplastos de lidocaína devem ser considerados como terapia de primeira escolha no tratamento da nevralgia pós-herpética da face devido a sua segurança e ao custo-benefício.

Palavras-chave: Anestésicos; Lidocaína; Herpes Zoster; Nevralgia.

Resumen

La neuralgia posherpética es una de las neuropatías más desafiantes. Hay muchas opciones de tratamiento con distintos grados de eficacia. El presente trabajo realizó una revisión sistemática sobre el uso de parches de lidocaína en el tratamiento de esta neuralgia. Se realizó una revisión sistemática siguiendo el protocolo PRISMA sobre parches de lidocaína en el tratamiento de la neuralgia postherpética. El protocolo fue registrado en el sistema PROSPERO. El metanálisis se creó con el software RevMan. Se incluyeron nueve artículos según los criterios de inclusión y exclusión. Se elaboró una tabla de los artículos incluidos y el motivo de la exclusión. Los parches de lidocaína son efectivos en el tratamiento de la neuralgia postherpética y son más seguros que otros medicamentos, lo que los hace útiles en pacientes ancianos con comorbilidades, donde el uso de otros medicamentos genera una serie de efectos adversos. Los parches de lidocaína deben considerarse como la terapia de primera elección en el tratamiento de la neuralgia facial postherpética debido a su seguridad y rentabilidad.

Palabras clave: Anestésicos; Lidocaína; Infección de herpes; Neuralgia.

1. Introduction

Post-herpetic neuralgia (PHN) is the most common complication of herpes zoster, an infection that results from reactivation of the varicella zoster virus. The cutaneous manifestations disappear completely after a variable time, however, there are situations where the pain persists even with complete remission of the lesions and must last more than three months to be classified as PHN. It affects about 50% of patients over the age of 50 with herpes zoster, which is considered a major public health problem in many countries with high treatment costs. Patients report constant pain or stabbing pain, and allodynia (Baron et al. 2009c), a change in pain perception.

The incidence of herpes zoster in Europe is high, affecting 10 in 1,000 people over the age of 80, and in those who have had an episode, the incidence of PHN is between 7 to 27% (Baron et al. 2009a). Some studies have reported that at least 90% of Americans by the age of 15 have been exposed to the virus, the same in the UK. In patients over 60 years of age, the quality of life deteriorates considerably, especially sleep, appetite, social life, and is the cause of many situations of anxiety and depression situations in a large percentage of affected patients. It can affect any anatomical region of the trunk, face or extremities, or even more than one region.

The PHN treatment is drug and / or surgical modalities and includes tricyclic antidepressants, gabapentin, pregabalin (anticonvulsants) and lidocaine patches. A second therapeutic line includes using opioids, tramadol, the subcutaneous use of botulinum toxin or corticosteroids, and capsaicin creams or patches, a chemical component obtained from peppers of the *Capsicum* genus. Articles report the use of patches based on non-steroidal anti-inflammatory drugs like piroxicam, but their use is not yet as routine as the other drugs already reported. Because it affects elderly patients who often have other comorbidities and are taking systemic drugs, systemic drug management for PHN may be compromised due to multiple drug interactions, primarily due to the central nervous system action of most drugs. Many of these side effects cause treatment to be interrupted, resulting in recurrence or even increase in pain, and many triggering depression, anxiety, insomnia, and a deterioration in quality of life (Campbell et al. 2002).

Lidocaine patches are a relatively new treatment modality for PHN, and the aim of the presente study is to evaluate, through a systematic review, to evaluate the effectiveness of these patches and their safety compared to other treatment modalities.

2. Methodology

Sorting of articles

Two authors carried out the research independently of one another (CRPJ and RG), from September 15 to October 2, 2020, using same strategy on two databases: MEDLINE (PubMed) and the Cochrane Library. The following bibliographic search strategy was used: [(lidocaine plaster) OR (lidocaine patch)) AND (postherpetic neuralgia)]. 826 articles were found on lidocaine patches, 98 on lidocaine plaster and 3039 on post-herpetic neuralgia. Grey literature search was not performed. After

excluding the screen by the title or abstract, 300 articles were obtained (150 from MEDLINE and 150 from the Cochrane library).

Duplicate articles were excluded using the Merge Duplicates command in the Mendeley software. Articles that have used a different type of patch, specifically capsaicin and piroxicam and; all discussions, reviews and systematic reviews. Only articles in English were included. However, no article on the year of publication was excluded because it is a relatively new drug. Articles evaluating the costs of treatment and its benefits were excluded as they did not directly rate the effectiveness of the patch. The same problem was the exclusion of articles that assessed the indirect opinion of professionals (pharmacies, hospital centers) rather than professionals who treated patients directly.

Studies with one or more identical authors and / or co-authors were excluded as it is not clear whether they used the same sample. Articles showing an obvious conflict of interest were excluded. Because the aim was to evaluate the effectiveness of lidocaine patches in the treatment of PHN, we excluded all articles that did not include the term PHN in the title or abstract. Articles reporting on neuropathic pain treatments in general or other specific pains such as trigeminal neuralgia, diabetic neuropathy, postoperative neuropathic pain, and polyneuropathy were excluded.

Only articles with patients 50 years and older were included because the incidence is rare in younger people and the effectiveness of patches in the treatment of PHN has been assessed. Of the 300 abstracts read, 36 articles were received. All 36 articles were read and, after reasonable exclusion (Table 1), nine articles were included in this work. This review was registered in the PROSPERO (International prospective register of systematic reviews) under the number CRD42021228932.

Table 1 - Excluded articles and reasons.

Reason	Autores
Case report	(Kontić et al. 2016)
Assessment of patients less than 50 years of age	(Goddard and Reaney 2018); (Wehrfritz et al. 2011)
Not directly related to the effectiveness of the lidocaine patch	(Kirson et al. 2010b); (Kirson et al. 2010a); (Smith et al. 2021) ;
Different patches used to treat NPH	(Gore et al. 2007)
The studies did not directly assess the clinical effectiveness of the drug, but rather responses from pharmacies, hospitals and / or medical centers	(Dakin et al. 2007) ; (Gudin et al. 2019); (Laurent et al. 2014); (Ritchie et al. 2010)
Review article, but the term did not appear anywhere in the title or search engine	(Bruckenthal and Barkin 2013); (Fashner and Bell 2011)
The studies confirmed the effectiveness of the patches, but the evaluation was not made specifically for analgesia, but for other issues.	(Campbell et al. 2002); (Pickering et al. 2014) ; (Wasner et al. 2005)
Studies in the same hospital / university center or in the same team. The latest article has been retained.	(Baron et al. 2009c); (Baron et al. 2009a); (Baron et al. 2009b); (Binder et al. 2009); (Hans et al. 2009); (Rehm et al. 2010); (Rowbotham et al. 1996); (Sabatowski et al. 2012); (Sabatowski et al. 2017)
Some of the authors have a clear conflict of interest	(Liedgens et al. 2008) ; (Obradovic et al. 2014); (Sabatowski et al. 2017)

Source: Own authorship.

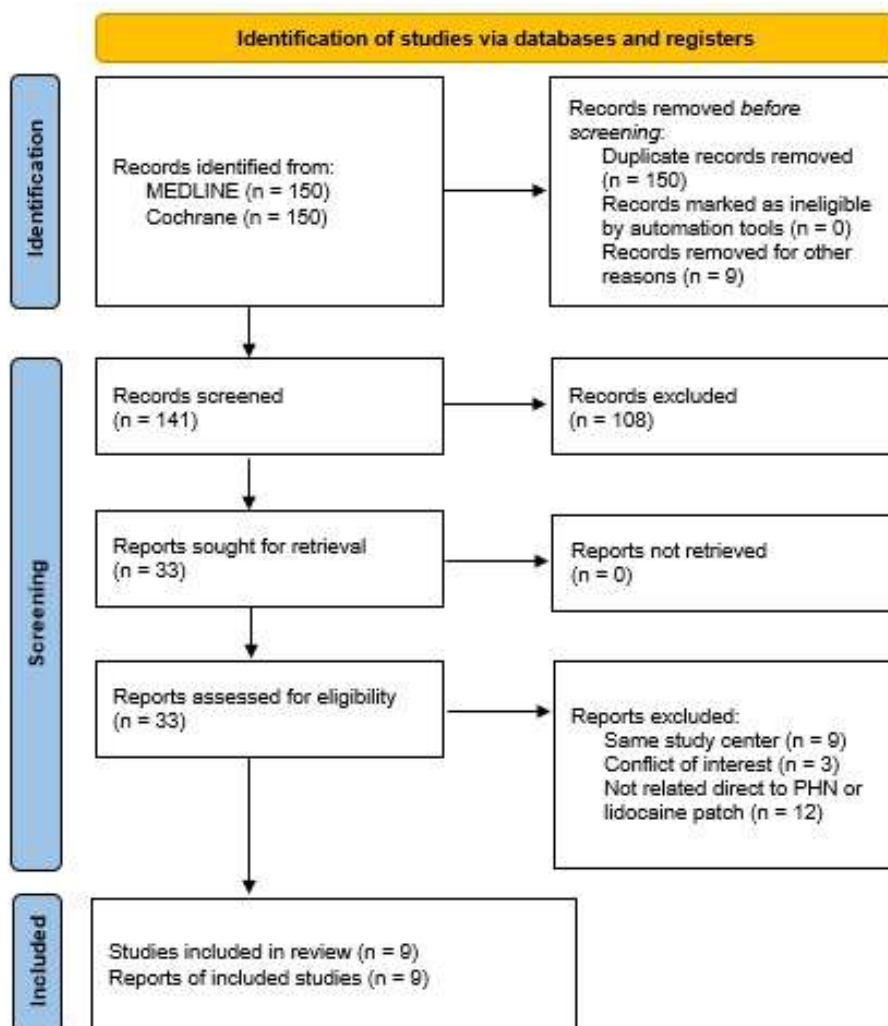
Risk of bias

The risk of bias was analyzed and carried out by two different reviewers (CRPJ and RG). Although all disagreements were resolved by consensus (Higgins et al. 2011), a risk of bias graph was created using Review Manager Software 5.3 software (Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2014). Following the Cochrane Library guidelines where it is possible to evaluate the work in low, high and uncertain risks (Pedrosa Viegas de Carvalho et al. 2013).

3. Results

Nine articles were included in this systematic review (Figure 1). The inclusion criteria used in the studies were: patients of any gender, age over 50 years, complaints of PHN for at least three months with pain level on the numerical estimation scale (VAS) greater than or equal to 4, on a scale that varies from 0 to 10 (Binder et al. 2016). This is just one of the pain intensity assessment scales and the most commonly used in this review (Lin et al. 2008; Malec-Milewska et al. 2015; Binder et al. 2016; Bursi et al. 2017). Some studies were multicenter (Nalamachu et al. 2013) and due to geographical simplicity most of them are from Europe (Clère et al. 2011; Binder et al. 2016; Bursi et al. 2017). None of the studies that were part of this review were conducted in a country with a tropical climate.

Figure 1 - Flowchart of articles.



Source: Own authorship.

There was a statistical predisposition to PHN in female patients. In only one study, this prevalence was higher in male patients (Casale et al. 2014), although the same was done with a shallow sample, only in eight patients. The predisposition was 58.72% in women and 41.28% in men, which has already been reported in some studies (Lu et al. 2018; Wang et al. 2020). The average size of the samples evaluated was 179.33 patients, from 8 (Casale et al. 2014) to 332 patients (Katz et al. 2002; Nalamachu et al. 2013). Some studies have not rated the effectiveness of patches in terms of the number of patients who showed some level of improvement; instead, it is less expensive compared to gabapentin (Dakin et al. 2007). The mean age of the examined patients was 71.92 years. Studies in patients under 50 years of age has not been used because PHN is rare in young patients. The age ranged from 20 years (Katz et al. 2002) to 96.6 years (Galer et al. 1999). There are reports that patients over 70 years of age showed insignificant pain reduction (Clère et al. 2011), the importance of using patches as the treatment of first choice once PHN was (Katz et al. 2002). A brief resume of some demographic data is available on Table 2.

Table 2 - Distribution of PHN in relation to the number of patients studied, age and gender.

Reference	Number of patients	Mean age	MAX age	MIN age	Men	Women
Binder et al., 2016	263	72,5	81	64	112	151
Bursi et al., 2017	212	72	92	45	93	119
Casale et al., 2014	8	77,75	84,85	70,65	5	3
Clère et al., 2011	273	73,2	85,1	61,3	115	158
Galer et al., 1999	32	77,4	96,6	62,05	14	18
Katz et al., 2002	332	71	20	99	133	199
Lin et al., 2008	42	64,04	79	47	19	23
Malec-Milewska et al., 2015	120	73,06	84,16	60,7	40	77
Nalamachu et al., 2013	332	71,2	85,1	57,3	134	198
TOTAL	1614	64,95			665	946
Media	179,33	Corrected media	71,92		41,28%	58,72%

Source: Own authorship.

Body weight is an important factor and must be taken into account when determining the number of patches used, therefore the Body Mass Index (BMI) was used as one of the assessment criteria in some of the articles evaluated (Casale et al. 2014; Binder et al. 2016; Bursi et al. 2017).

The vast majority of articles reported using lidocaine patches for an uninterrupted period of 12 hours, generally used at night to improve the quality of sleep, alternating with another 12-hour rest period. This 12-hour rest period is necessary because of the risk of high serum lidocaine concentrations, which can lead to serious side effects such as severe hypotension. The vast majority of the articles do not explain why this 12-hour rest lasts (Binder et al. 2016) despite the fact that this time is described in the manufacturer's recommendations. However, studies claim that long-term exposure to lidocaine does not cause complications or reduce the safety of use (Galer et al. 1999; Nalamachu et al. 2013; Bursi et al. 2017). Among the side effects considered mild and common, there may be a burning sensation at the site of the patch, itching, rashes, local irritation, dizziness, nausea, blurred vision, and hypotensive crises.

According to the VAS scale, the mean pain intensity was 6.19, and When using lidocaine patches the mean pain reduction was 2.81, and reached a maximum of -5 (Malec-Milewska et al. 2015), which can be considered an effective treatment (Clère et al. 2011; Casale et al. 2014). One study assessed the reduction in the extent of pain rather than the reduction in pain intensity (Casale et al. 2014). While others examined the effectiveness of patches not in terms of reducing pain intensity, but rather because of reducing or stopping pain medication (Clère et al. 2011).

The average number of patches used, unlike systemic drugs, tends to decrease over time, a major factor that can be critical in the choice of patches due to the lower risk of side effects with prolonged use of systemic drugs (Galer et al. 1999).

Systemic drug treatment is one of the first options in the treatment of PHN and the most widely used (Katz et al. 2002). Due to the high average age of the patients and the pharmacology of the drugs used in the treatment of PHN, some side effects occur with a certain frequency. These side effects can be exacerbated and more common by using other systemic drugs that are already used to treat other pathologies, and cause drug interactions. Drugs used in the treatment of PHN are pregabalin and gabapentin, drugs analogous to gamma-amino-butyric acid (GABA), used as an anticonvulsant and used to treat peripheral pain and fibromyalgia. These drugs have several side effects, notably fatigue, dizziness and lightheadedness (Binder et al. 2016).

Lidocaine patches have been reported to have a better clinical response when compared to pregabalin and / or gabapentin (Nalamachu et al. 2013). In studies with a placebo patch control group, lidocaine patches were superior in pain relief (Malec-Milewska et al. 2015; Binder et al. 2016). Several comparisons have been made between lidocaine patches and pregabalin, and even if the clinical outcome of both are similar, lidocaine patches have fewer side effects in addition to having a less effective onset of analgesia (Binder et al. 2016). They can be used as monotherapy for PHN treatment, but when combined with other systemic drugs, they provide more effective analgesia (Binder et al. 2016). Lidocaine patches are likely to have side effects, but in a much smaller percentage than systemic drugs as the vast majority are considered mild or moderate (Clère et al. 2011; Nalamachu et al. 2013). Serious side effects are likely related to pre-existing comorbidities in the patient and not to the use of the patch itself (Binder et al. 2016).

The improvement in pain intensity is gradual and represents a decrease from good to severe for a period of time that can vary from two days (Binder et al. 2016) to three months (Casale et al. 2014). This effectiveness varies between 60% (Casale et al. 2014), 85% (Clère et al. 2011) to 88% (Binder et al. 2016). The decrease the pain in the facial area seems to be less than that found in other anatomical regions, but there is only one article about it (Nalamachu et al. 2013). There are reports in which the percentage of effectiveness was not stated, only that the plasters in the treatment of PHN are effective in some cases more effective than other therapies. The use of patches is associated with a significant reduction or even discontinuation of systemic medications, with only maintaining control of analgesia with the use of patches (Katz et al. 2002; Clère et al. 2011; Casale et al. 2014). It has been shown that the improvement in pain leads to a general improvement in function, sleep and quality of life. Because many patients tend to develop a depressive state due to severe and persistent pain.

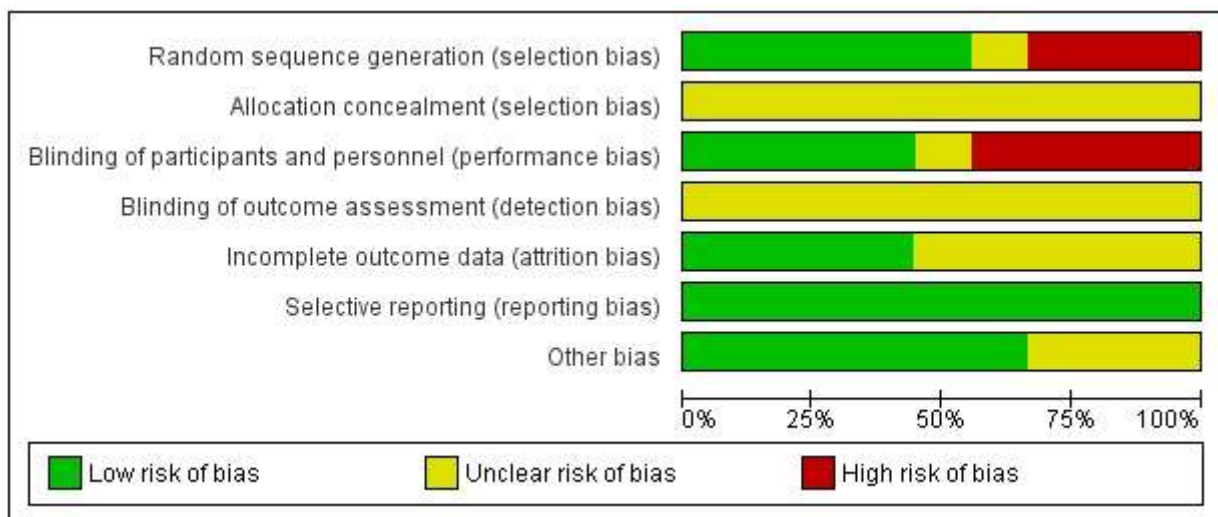
Some studies have shown the predisposition to PHN related to some pathologies (Malec-Milewska et al. 2015) including diabetes mellitus (DM), malignant neoplasms, nephropathies, heart disease, hypercholesterolemia, osteoporosis, osteoarthritis and chronic steroid use. DM presents itself as the most important systemic change that triggers NPH (Malec-Milewska et al. 2015) and not only NPH but also peripheral polyneuropathies as the main cause. This high correlation between DM and NPH is due to changes in nerve conduction in diabetics (Metsker et al. 2020).

According to some authors, it is the first choice in PHN cases because of its cost-effectiveness compared to other drugs, safety and tolerability profile (Katz et al. 2002; Binder et al. 2016) and longer use of patches better than other drugs for the same reasons.

The studies included in this systematic review were very heterogeneous in terms of data collection and analysis, with quantitative and / or qualitative analyzes. Although they inferred the effectiveness of lidocaine patches in PHN treatment, the performance of the meta-analysis remains questionable. Even some of the analyzes used in these cases would not be effective because the sensitivity analysis requires studies with certain characteristics and the meta-regression must adhere to the minimum limit of ten studies (Pereira et al.). Articles measure the effectiveness of lidocaine patches in other ways, including number of patches used at the same time, reducing the number of simultaneous use of analgesics, percentage of patients with less pain, patient satisfaction, comparing side effects with other drugs. This makes creating a forest plot impossible.

The risk of bias of the articles included in the study (figures 2 and 3) can be analyzed with the RevMan 5.3® software (Cochrane Library). When analyzing the figures, it should be noted that the studies present a risk of bias in terms of both randomization and blinding of the studies.

Figure 2 - graph of risk of bias in the articles analyzed using the RevMan 5.3® software.



Source: Own authorship.

Figure 3 - summary of risk of bias in the articles analyzed using the RevMan 5.3® software.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Binder et al, 2016	+	?	+	?	+	+	?
Bursi et al, 2017	+	?	+	?	?	+	?
Casale et al, 2014	-	?	-	?	+	+	+
Clère et al, 2011	+	?	-	?	+	+	?
Galer et al, 1999	+	?	+	?	?	+	+
Katz et al, 2002	-	?	-	?	?	+	+
Lin et al, 2008	+	?	+	?	+	+	+
Malec-Milewska et al, 2015	?	?	-	?	?	+	+
Nalamachu et al, 2013	-	?	?	?	?	+	+

Source: Own authorship.

4. Discussion

A decrease in effectiveness only occurred in patients over 70 years of age (Clère et al. 2011), but the treatment was effective in both young patients and in patients between 50 and 70 years of age. The vast majority of the authors reported neither a greater predisposition to PHN between the sexes nor that the treatment was more or less effective depending on the sex.

The use of patches should be done as early as possible, as it is the treatment of first choice for some authors (Katz et al. 2002), as the patient feels the pain and the time of application is related to the success of the treatment. The recommendation for use is a maximum of three patches at the same time with a maximum duration of use of 12 hours, so that there is no increase in side effects. This period should be the patient's most painful complaint, regardless of whether at night or during the day. The number of patches tends to decrease with time of use and, in some cases, there have been reports of treatment interruption due to the high effectiveness of the patches (Katz et al. 2002).

Particular caution should be exercised in patients taking other systemic drugs, with comorbidities or with a low BMI, using the proportion of one patch per 30 kg body weight. There is no other way to adjust the dose other than concerning weight. Patients with diabetes mellitus are the most susceptible to chronic neuralgia, and the use of patches is an effective and safer form of therapy due to the continued use of systemic drugs.

The literature categorically assesses the effectiveness of patches. Compared to other systemic drugs, be they anticonvulsants, antidepressants, anti-inflammatories or analgesics, they have superior efficacy, not only because of their effectiveness in analgesia, but also because of their more unique safety profile, which causes fewer side effects, regardless of the measurement scale used, sex, comorbidities, age, affected anatomical region and BMI. For many, it is the drug of choice.

The clinical implications of this study include the cost-effectiveness of using patches. Their use is advantageous in comparison to other therapeutic modalities, because even if it is not an inexpensive drug, the other treatment alternatives are more expensive for the healthcare system. Using patches can provide financial relieve for some healthcare systems that are already very committed. Some of the limitations of this study are due to different pain scales used in the included articles and difficulties in assessing and measure pain due to its subjectivity.

5. Conclusion

The literature confirms the superiority of lidocaine patches in the treatment of PHN considering the issues of efficacy (analgesia, improved sleep and quality of life), safety (fewer side effects) and cost compared to systemic drugs available today. It should be the therapy of choice regardless of gender, comorbidities, age and BMI. Although it is not fully effective, it can and should be used in conjunction with other systemic drugs.

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