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Phenytoin Topical as Pain Neuropathic Therapy: A Scoping Review

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Abstract

Background: Neuropathic pain is a type of pain that can cause prolonged pain in patients. Oral treatment takes a long time and can cause side effects, which can further reduce patient compliance with therapy. Topical treatment is a more acceptable alternative because it has minimal systemic side effects. Phenytoin is an anticonvulsant drug that can be used as a therapy for neuropathic pain. The side effects of oral phenytoin are minimized by using topical preparations.
Objective: To obtain information on the effectiveness of topical phenytoin in neuropathic pain. Long-term goal, conduct clinical trials in patients and make topical phenytoin preparations in collaboration with one of the PBF (Large Pharmaceutical Companies) in Indonesia.
Methods: Three electronic databases were searched on January 13, 2022: Google Scholar. PubMed and ScienceDirect. All relevant literature was included after screening according to the PRISMA statement. Data obtained were synthesized based on PICO (population, interventions, comparisons, and outcomes).
Results: This paper examines case reports, case series, and pre-existing research articles in which topical phenytoin significantly reduces neuropathic pain.
Conclusion: Topical phenytoin may be an alternative in the selection of neuropathic pain therapy due to its minimal side effects compared to oral therapy. However, further studies need to be conducted to compare with other topical anticonvulsants.
Keywords: Topical Phenytoin, Anti-seizure, Pain, Neuropathic

Introduction

Damage to peripheral and central nervous system (CNS) nerve tissue results in neuropathic pain. This discomfort may manifest in the absence of tissue damage or even after tissue damage has healed (Bouhassira, 2019). Numerous polyneuropathic disorders can result in peripheral neuropathic pain. Excessive sensory nerve activity caused by the production of inflammatory chemicals surrounding the injured neuron results in neuropathic pain. Neuropathy symptoms as burning, tingling, cold pain, electric shock, itching, hyperalgesia, and allodynia are brought on by these pro-inflammatory mediators that make nerve fibers and nociceptors more sensitive (Hesselink & Kopsky, 2017; Purba, Jan Sudir; Aninditha, 2017). According to epidemiological research, 7–8% of people in the general population experience neuropathic pain, which accounts for 20%–25% of those with chronic neuropathic pain (Bouhassira, 2019).

A moderately severe chronic condition known as neuropathic pain can cause or worsen depression, thereby negatively impacting quality of life, daily functioning, work, and sleep quality (Coderre, 2018; Kopsky, et al., 2021). Oral antidepressants (such as amitriptyline and duloxetine) and anticonvulsants (such as pregabalin and gabapentin) are first-line treatments for neuropathic pain. Second- and third-line treatments include tramadol and strong opioids (such as oxycodone) (Hesselink & Kopsky, 2017). Unfortunately, neuropathic pain can worsen over time, although conventional treatments can alleviate some of the pain. Early studies on how drugs work are better than patients' perceptions of their rapid effects. Most oral co-analgesics for neuropathic pain take days to weeks to work properly. This can lead to decreased compliance (Hesselink & Kopsky, 2018). It can also be caused by the lack of expected effect or the onset of intolerable side effects, such as sedation, dizziness, depression, nausea, constipation, and others. In

addition, continuous use of oral analgesics can lead to side effects such as drug interactions, nephrotoxicity, and hepatotoxicity (Hesselink & Kopsky, 2017).

Topical analgesics present an intriguing choice because they avoid systemic side effects by affecting only epidermal nerve endings without reaching the bloodstream (Kopsky et al., 2021). There is evidence that peripherally acting drugs, such as lidocaine (in the form of topical creams or patches), can reduce peripheral sensitization by blocking peripheral input. The main disadvantage of patches is that they are difficult to use on some parts of the body, such as the feet. Because they are difficult to understand, especially for older people, compliance with their use is considered suboptimal. Lacking this disadvantage, topical creams are easier to use. Analgesics such as ketamine, amitriptyline, baclofen, gabapentin, clonidine, and so on have been used singly or together (Hesselink & Kopsky, 2017).

As a wide sodium channel blocker and one of the earliest anticonvulsants ever found, phenytoin is one of the oldest active medicinal compounds. In this medicine category, it remains one of the gold standard medications. Chronic pain is one of the many non-epileptic disorders that anticonvulsant drugs are used to treat. In animal pain models, phenytoin is utilized for optimization and has also been acknowledged as a therapy option for neuropathic pain (Heselink & colleagues, 2018).

Some other topical analgesic creams offer significant pain alleviation, but at times, patients need to use these analgesic creams more frequently to maintain the analgesic effect (Hesselink & Kopsky, 2017). Research examining topical phenytoin for wound healing therapy found no signs of systemic absorption or toxicity. Additionally, topical phenytoin provides pain relief, with effects starting in roughly 15 minutes. No levels of phenytoin were found in the plasma after the application of 10% and 20% phenytoin formulations on undamaged skin, even when large doses of phenytoin, up to 670 mg per use, were applied (Kopsky et al., 2022).

This research is expected to be useful as a scientific reference, adds the latest information about developments in medical science, and can be used as a reference regarding the role and application of topical phenytoin as an analgesic in neuropathic pain patients.Topical phenytoin therapy preparations have not been routinely recommended as analgesics for neuropathic pain. From various literature that we have conducted in preliminary studies, it was found that topical phenytoin is able to reduce neuropathic pain with a rapid onset, and no side effects were found.

Method

This study used a scoping review study design conceived to collect all research on topical phenytoin and neuropathic pain, along with reports of more extensive research (studies, case series, or case report papers), and to review and analyze their findings. Articles for this review were searched using online databases such as Google Scholar. PubMed and ScienceDirect will be used to search with the search terms (“phenytoin cream” OR “topical phenytoin”) AND (“neuropathic pain” OR “neuropathic pain” OR “neuralgia”) to search for evidence-based medical journals.

Eligibility criteria for abstract articles were: articles mentioning topical phenytoin for neuropathic pain, articles associating topical phenytoin with neuropathic pain, no age restriction, no gender restriction, no country or race restriction, English language articles only, comprehensive empirical studies (non-targeted reviews) and case series or case reports reporting the use of topical phenytoin for neuropathic pain. As the use of topical cream formulations for neuropathic pain is a new treatment, there is no time restriction on the literature search. It is desirable to have access to all literature written on the topic up to the time of the study. Studies are excluded if they are not original research, such as reviews, commentaries, research protocol, or theoretical papers. Non-human studies, such as animal research, are also excluded, as are studies involving populations or conditions that do not align with this review theme’s focus. Studies published in non-English paper, or those for which full-text access is unavailable, also are not included.

The literature search through online databases was conducted on 13 January 2022. The review will be carried out jointly by two researchers based on titles and/or abstracts. If duplicates are identified, the review will continue by checking whether the title or abstract complies with the eligibility criteria. Once papers are received that meet the eligibility criteria based on title and abstract, the full text will be read to check whether they comply with the eligibility criteria. Disagreements regarding the eligibility of papers with eligibility criteria will be resolved through discussion between the four researchers. Papers meeting the eligibility criteria will be rigorously evaluated using tools appropriate to the study design. Variables used in this study were analyzed using PICO (Patient, Intervention, Comparison, Outcome).

Result and discussion

The search for articles according to keywords obtained 96 articles, which were then narrowed down to 90 articles due to the duplication of 6 articles. The next selection was made by reading the abstracts and full texts, resulting in 26 articles. Furthermore, 12 articles were excluded: 3 articles did not specifically discuss topical phenytoin, 2 articles offered expert opinions, 5 articles were research reviews, 1 article was a research protocol, and 1 article explained the topical phenytoin hypothesis. In this study, we used 14 articles consisting of: 2 research articles, 5 case series, and 7 case reports, which we then carried out a PICO analysis on and reviewed to obtain information on the effectiveness of topical phenytoin in neuropathic pain therapy.

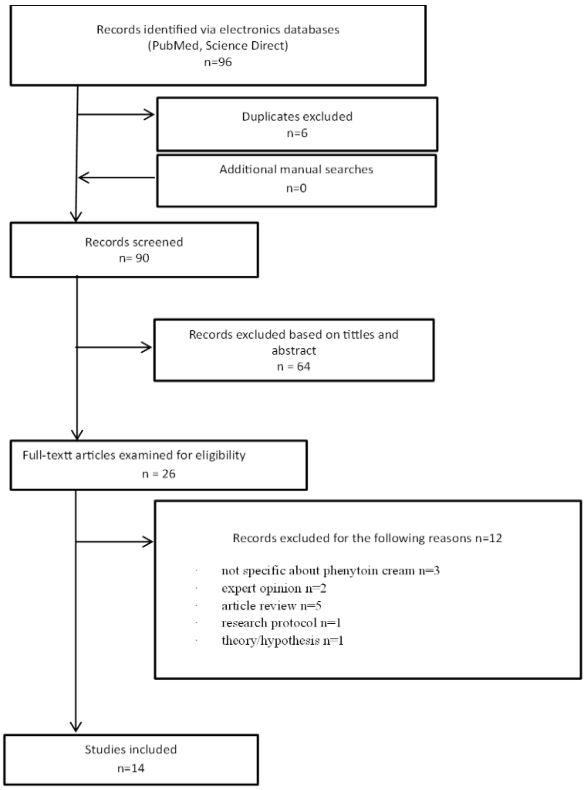

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the literature search results and review process.

Table 1. Selected study used to discuss about Phenytoin Topical as Pain Neurophatic Therapy

No	Article number	Author, year	Title	P	I	C	O
1.		Kopsky DJ, 2018	"Phenytoin Cream for the Treatment for Neuropathic Pain: Case Series"	70 Subjects with neuropatic pain	Phenytoin cream 5 (n : 9 patient) or 10% (71 patient)	Placebo	On average, it was able to relieve pain in 16.3 minutes, the ability to relieve pain for 8.1 hours and was able to reduce pain by 61.1% as measured by the Numeric Pain Scale (NRS). There was a significant reduction in pain compared to placebo in the administration of

							topical phenytoin 10% ($p < 0,01$).
2.	(1)	Hesselink JMK, Kopsky DJ, 2018	"Neuropathic Pain due to Chronic Idiopathic Axonal Neuropathy: Fast Pain Reduction After Topical Phenytoin Cream Application: Case Study"	A 56-year-old patient with chronic idiopathic axonal polyneuropathy (CIAP)	Phenytoin cream 10%	Placebo	After 20 minutes of treatment, it was found that the pain in the right foot, which was treated with placebo cream, did not change, and the NRS score remained at 7, while the left foot, which was treated with phenytoin cream 10%, experienced a change in the NRS score from 7 to 2.
3.	(4)	Kopsky DJ, Hesselink JMK, 2017	"Topical Phenytoin for the Treatment of Neuropathic Pain: Case Series"	Case I: A 69-year-old patient with neuropathic diabetic pain Case II: a 71-year-old patient with a ombination of pain	Phenytoin cream 10% (n: 2) atau 5% (n: 3)	Case I: ketamine cream 10% Case II: baclofen 5%, amitriptyline 5%, and clonidine 0.2% Case III: baclofen 5%	Case I: in the administration of ketamine 10% the NRS score is reduced to 3 within 25 minutes and lasts for 6 hours, in the administration of phenytoin cream 5% the NRS score is reduced to 3 with an onset of 5 minutes and lasts for 8 hours, while in the administration of phenytoin cream 10% can reduce the NRS score to 0 with a onset of 5 minutes and lasts at least 12 hours. Case II: on administration of baclofen 5%, amiptriptyline 5%, and clonidine 0.2%, the NRS score was reduced from 8 to 2 -4. In the administration of phenytoin cream 5% NRS score was reduced from 8 to 3 with an onset of 20 minutes, the effect lasted 5 hours longer than other analgesics. Case III: with the administration of baclofen 5 % the NRS score was reduced from 7 to

							3 with an onset of 20 minutes, with the administration of phenytoin 5% the NRS score was reduced from 7 to 0 with an onset of 30 minutes and lasted for 4 hours, while with the administration of phenytoin 10% the NRS score was reduced from 7 to 0 with an onset of 10-15 minutes and lasted for 6 hours.
4.	(5)	Hesselink JMK, 2018	"Topical Phenytoin in Painful Diabetic Neuropathy: Rationale to Select a Non-selective Sodium Channel Blocker: Case Report"	A 61-year-old man with symmetrical diabetic polyneuropathy pain	Phenytoin cream 5%	-	Administering phenytoin cream 5% with 1 finger or 0. 6 grams for 60 minutes can reduce pain measured using a nutritional risk screening score from 8 to 4 and the effect lasts for 8-12 hours.
5.	(6)	Kopsky DJ, 2020	"Usefulness of a Double-Blind Placebo-Controlled Response Test to Demonstrate Rapid Onset Analgesia with Phenytoin 10% Cream in Polyneuropathy"	12 adult patients with symmetrical polyneuropathic pain who had a pain intensity of ≥ 4 measured using NRS	Phenytoin cream 10%	Placebo	● Of the 12 patients, there were 6 patients who were included as respondents (there was a decrease of ≥2 points from the NRS score or there was a difference of ≥1 points from the NRS score between the area of administration of phenytoin cream 10% and placebo). ● Compared to placebo, phenytoin cream 10% has a greater pain reduction rate. There was a significant reduction in pain. With an average difference from the pain reduction score of 1.3% CI: 1.1

6.	(7)	Hesselink JMK, 2018	"A Case of Wasp-induced Pain Treated with Topical Phenytoin Cream: Case Report"	A 64-year-old patient with pain from a bee sting	Phenytoin cream 10%	-	Administration of phenytoin cream 10% with 1 finger or 50 mg for 10 minutes causes a change in NRS score from 5-6 to 3, then after 20 minutes the pain disappears.
7.	(8)	Hesselink JMK, Kopsky DJ, 2017	"Burning Pain in Small Fibre Neuropathy Treated with Topical Phenytoin: Rationale and Case Presentations"	Case I: a 74-year-old patient with CIAP pain in both legs Case II: a 48-year-old patient with CIPN pain in the legs Case III: a 61-year-old patient with diabetic polyneuropathic pain in both legs Single blind test: 2 adult patients with pain in Small Fiber Neuropathy (SFN)	Phenytoin cream 5%	Case I: Amitriptilin cream 10%, baclofen cream 5%, and lidocain cream 3%, combination of isosorbid in nitrate cream 0.4% Case II: Amitriptilin cream 10% Case III: - Single blind test: Placebo	Case I: the combination of amitriptylin cream 10%, baclofen cream 5%, and lidocaine cream 3% was not enough to reduce pain, while phenytoin cream 5% could reduce the NRS score from 6 to 1, with a onset of 10 minutes and the effect lasted for 5 hours Case II: the administration of amitriptylin cream 10% could reduce the NRS score decreased from 8.5 to 0, But the effect only lasts for 1 hour. Meanwhile, with the administration of phenytoin cream 5%, he pain can be completely eliminated and the effect lasts for 3-4 hours, with an onset of 15 minutes Case III: with the administration of phenytoin cream 5% can completely eliminate pain with an onset of 1 hour Single blind test: in the administration of phenytoin cream 5% can reduce pain by 30%
8.	(9)	Hesselink JMK, Kopsky DJ, 2018	"Fast Onset of Relief After Topical Phenytoin in Neuropathic Pain after	6 patients with CIPN pain.	Phenytoin cream 10%	Amiptriptilin 10%	In the administration of phenytoin cream as much as 0.9 grams, 4 out of 6 patients

			Chemotherapy: Case Report”				experienced a >50 % reduction in pain. The other 2 cases experienced a reduction in pain of about 30%. In most cases, the onset is about 30 minutes and in 1 person there is a rapid onset of about 2 minutes. The duration of the effect lasts between 2.5- 70 hours. Due to the unbalanced distribution, the researchers also reported a median and the duration of the effect, 9 .0 hours (3.6; 35.5) and the onset of real pain relief, 11.0 minutes (6.5; 31.3). interquartile range (IQR)
10.	(11)	Kopsky DJ, Hesselink JMK, 2018	“Phenytoin Cream for the Treatment of Neuropathic Pain: Case Series”	70 patients With neuropathic pain	Phenytoin cream 5% and 10%	Placebo	● The mean reduction in pain in NRS scores with the use of phenytoin cream was statistically significant with a reduction of 4.5 (CI: 4.0 to 5.0, p < 0.01).0.01) ● In 12 people who were single-blind tested, after 30 minutes, the area where phenytoin cream was applied 10% experienced a reduction in pain of 3.3 (CI: 2.3 to 4. 4, p < 0.01) while in the area where placebo was applied, there was a reduction of 1.1 (CI: 0.4 to 1.9, p < 0.05). This difference was

very significant ($p < 0.01$). Meanwhile, in open treatment, patients experienced a reduction in pain to 4.0 on the NRS score (CI: 2. 8 to 5.1, $p < 0.01$) compared to baseline 7. 3 (SD: 0.4).

- The average onset after the use of phenytoin cream 5% and 10% is about 15 minutes. The average effect has a duration of almost 5 hours for 5% phenytoin cream while for 10% phenytoin cream has an effect duration of more than 8 hours. However, the 3.8-hour difference in the two groups was not statistically significant ($t(66) = 1.2$, $p = 0.2$) when tested using an independent t-test.

- After the use of phenytoin cream for 1-2 weeks after use, about 1.5-3 hours after the last use, no phenytoin was found in the plasma of the 16 patients examined, even after the use of 6.7 grams of phenytoin cream 10%

								cream in 1 case.
11.	(12)	Kopsky DJ, Hesselink JMK, 2018	"Phenytoin in Topical Formulations Augments Pain Reduction of Other Analgesics in the Treatment of Neuropathic Pain"	Case I: a 57-year-old patient with SFN Case II: a 69-year-old patient with diabetic pain Case III: a 63-year-old patient with CIAP Case IV: a 67- year-old patient with CIPN Case V: a 48-year-old patient with CIPN Case VI: a 63- year-old patient with *Guillain-Barre syndrome*	Case I: phenytoin cream 10% Case II: phenytoin cream 10% Case III: phenytoin cream 5% Case IV: phenytoin cream 10% Case V: phenytoin cream 5% Case VI: Combination of phenytoin cream 5% dan baclofen cream 5%	Case I: ketamine cream 10% Case II: ketamine cream 10% Case III: clonidine cream 0,2% Case IV: combination of phenytoin cream 10% and baclofen cream 5% Case V: amitriptilin cream 10% dan combination of henytoin 5% + amiptriptilin 10% Case VI: baclofen cream 5%	Case I: 10 minutes of 10% phenytoin cream can reduce pain, adding 10% phenytoin cream to the area that has been given ketamine can eliminate tingling and can reduce the NRS score from 6.5 to 3 within 5 minutes. This improvement effect lasted for 24 hours. Case II: administration of ketamine cream 10% cream reduces pain from 9 to 5.5 on the NRS score, with an onset of 25 minutes and duration of effect for 6.5 hours. Adding phenytoin cream 10% to the area treated with ketamine cream 10% produces an onset of about 5 minutes and can reduce the NRS score by 2.5 and the effect extends to 11 hours. Case III: clonidine cream 0.2% can reduce the NRS score from 5 to 2.5 after 15 minutes of administration. The duration of the effect only lasted 6 hours. After adding phenytoin cream 5% to the area given clonidine cream 0.2%, the onset lasted 5 minutes, and the NRS score was reduced from 2.5 to 0. The duration lasted for 10 hours. Case IV: The left leg applied with phenytoin cream

							10% experienced a reduction in pain from 4 to 3, while the application of phenytoin cream 10% and baclofen cream 5% on the right leg reduced pain from 4 to 1 with an NRS score. Case V: Amitriptyline cream 10% can reduce the pain score within 8 minutes to 0 on the NRS, although only 1-1.5 hours. The use of phenytoin cream 5% can relieve pain completely with a duration of 3.5 hours after applying for 15 minutes. The combination of phenytoin cream 5% and amitriptyline cream 10% relieved pain completely, with a total prolonged effect of 8 hours and an onset of 3 minutes. Case VI: Baclofen cream 5% relieves pain completely, but should be applied 2-4 times at night. The combination of phenytoin cream 5% and baclofen cream 5% prolonged the effect of pain reduction and only one time use before bedtime.
17.	(19)	Hesselink JMK, Kopsky DJ, 2017	"Topical Phenytoin Cream Reduces Burning Pain Due to Small Fiber Neuropathy in Sarcoidosis"	patient case of burning pain and sleep disturbances due to small fiber neuropathy (SFN) in sarcoidosis	phenytoin 10% cream	Single blind response test: Placebo	Burning pain was reduced by 50% to 60%, resulting in a much improved sleep.

18.	(20)	Hesselink JMK, 2018	"Treatment of Painful Diabetic Neuropathy in SubSaharan Countries: Bottlenecks and Opportunity for the Repositioning of Phenytoin as a Topical Treatment: Case Report"	>100 patients with Pain Diabetic Neuropathy (PDN)	Phenytoin cream	Placebo	• After an open response test, the application of phenytoin cream on one leg and comparison with the other leg was not given the intervention. There was a decrease of at least 2 points in NRS in about 20 minutes to 30 minute. • Then a placebo is added to the response test, applied to one leg, while phenytoin cream is applied to the other leg in a single Blind. • Categorized as a respondent, if after 15 to 30 minutes, the patient experiences pain loss of at least 2 points on the NRS between phenytoin cream and placebo
19.	(21)	Russell AL, Kopsky DJ, Hesselink JMK, 2020	"Phenytoin Cream for the Treatment of Sciatic Pain: Clinical Effects and Theoretical Considerations: Case Report"	A 55-year-old patient with sciatic pain	Phenytoin cream 20%	-	• Giving 20% phenytoin cream to the painful area as much as 1.5 grams can lower the NRS score from 9 to 1, with a 30-minute onset and lasting effect resistance of 5-6 hours • However, sensory loss in the area experiencing pain cannot be changed by giving phenytoin

							cream 20%. No plasma levels of phenytoin were detected after two days of use of pheynitoin cream 20%, with blood sampling 3 hours after the last application.
20.	(25)	Kopsky DJ, Hesselink JMK, 2018	"Single-Blind Placebo-Controlled Response Test with Phenytoin 10% Cream in Neuropathic Pain Patients"	21 patients with localized neuropathic pain who had the same pain scale in at least 2 different areas and had an NRS score of ≥4	Phenytoin cream 10%	Placebo	• Of the 21 patients, there were 15 patients (71.45%) who were included as respondents (experienced a difference in NRS score change of ≥ 2 points between the area of administration of phenytoin cream 10% and placebo during 30 minutes of administration). • The mean reduction in NRS score in the area given 10% phenytoin cream was 3.3 (SD: 1.3) and in the placebo area 1.2 (SD: 1.1) over a period of 30 minutes • The mean percentage difference in pain reduction between phenytoin cream 10% and placebo was 33.2% (SD: 17.6., there was a significant difference (Z = -3.9, p < 0.001) between

	scores. McNemar 's exact test determined that there was a statistically significant difference in the proportion of MPR50 after the application of phenytoin cream 10% and placebo, p = 0.002, the same was also the case for MPR30, p < 0.001
	● Of the 21 patients, therewere 6 patients who saw phenytoin levels in plasma after 1-2 weeks of applying phenytoin cream 10%. Plasma sampling is carried out. 5-3 hours after the last application. No plasma phenytoin levels were detected (below the detection limit). In the other 10 patients, no plasma levels were detected even after the application of 6.7 g of phenytoin cream 10% in one case.

Based on previous studies, topical phenytoin can significantly reduce pain, where pain is measured using the Numeric Pain Scale (NRS). In this study, it was also found that different concentrations of topical phenytoin used for neuropathic pain therapy can result in different outcomes such as: onset, duration, and NRS score reduction.

Topical phenytoin has a pain-relieving effect, with an onset of effect of about 15 minutes. After using 10% and 20% phenytoin creams on intact skin, no measurable plasma concentrations of phenytoin were found, even when applying large doses of up to 670 mg at a time (Kopsky et al., 2022).

This study evaluated the effectiveness of topical phenytoin for managing various types of neuropathic pain, including diabetic neuropathy, chronic idiopathic axonal polyneuropathy (CIAP), chemotherapy-induced

polyneuropathy (CIPN), bee sting pain, small fiber neuropathy (SFN), and sciatic pain, compared to placebo and other topical analgesics such as ketamine 10%, baclofen 5%, clonidine 0 2%, lidocaine 3%, isosorbide dinitrate 0.4%, and amitriptyline 10%. The study reported that topical phenytoin resulted in overall pain reduction, decreased allodynia, and improved sleep quality (Kopsky et al., 2022).

Neuropathic pain is characterized as pain that directly results from damage to the somatosensory system. The skin is linked to the affective aspect of neuropathic pain. The epidermis is mainly supplied by non-peptidergic nociceptors, C-type nerve fibers, which are identified by immunohistochemical and molecular markers such as calcitonin gene-related peptide (CGRP), substance P, ion channels, receptors of the transient receptor potential (TRP) family, and endocannabinoid receptors such as CB1. Studies in mice with sciatica nerve lesions show that non-peptidergic nociceptors require a longer healing time compared to peptidergic nociceptors (Meregalli et al, 2022).

The local inflammatory component of neuropathic pain leads to sensitization of the peripheral nerve fibers. Damage and metabolic stress of these nerve fibers promote increased production of proinflammatory mediators such as cytokines and interleukins. Both affect peripheral and central nerve fibers and non-neuronal cells that cannot be excited by action potentials (Raja et. al. 2023). Peripheral nerve endings, keratinocytes and immune cells express ion channels and receptors and release many signaling molecules to create complex interactions (Kocot-K et.al., 2021). Increased excitability towards peripheral nerve fibers leads to increased neurotransmitter production in the spinal cord, associated with central sensitization in the form of neuropathic pain. Effective blockade of the considered input can prevent the occurrence of central sensitization and neuropathic pain (Finnerup et. al. 2020).

Keratinocytes establish a protective framework that encompasses peripheral nerve endings within the epidermis, facilitating interactions among themselves. The presence of neuro-activators and voltage-gated ion channels in the epidermis aids in autocrine and paracrine signaling between keratinocytes and nerve networks, which then impacts sensory signaling.

For example, light activation of keratinocytes through genetically engineered rodopsin channels produces a withdrawal reflex, similar to a pain stimulus. The activity occurs in conjunction with electrical signaling in the nerve, even though the nerve cell itself is not light sensitive.

A separate animal study demonstrated that capsaicin stimulation in mice, where TRPV1 receptors were expressed exclusively on keratinocytes and not on peripheral nerves, resulted in paw-licking reflex behavior and conditioned place rejection. In another animal model, stimulation of cannabis CB2 receptors on keratinocytes, but not on peripheral nerves, produced an indirect antinociceptive effect through the release of β-endorphin from keratinocytes. These findings provide clear evidence that the activation of keratinocytes can trigger the stimulation of peripheral sensory nerve endings within the epidermis (Kopsky et al., 2022).

Phenytoin works through several mechanisms, namely blocking Nav receptors, L-VGCC receptors, modulating GABAAR receptors and having anti-inflammatory effects (Kocot-K et.al., 2021). However, the main mechanism of phenytoin is the inhibition of ion channels (Kocot-K et.al., 2023; Hesselink, J. M. K., & Notermans, N. C. 2018). Phenytoin inhibits several sodium channels by binding to the inner vestibule of the channel pores. This affinity allows phenytoin to bind to almost all types of sodium channels (Nav1.1, Nav1.3, Nav1.5, Nav1.6, Nav1.7, Nav1.8, and Nav1.9 (Hesselink, 2018).

Nav receptors, which are the main targets of phenytoin, are extensively distributed on both peripheral nerve endings and keratinocytes. In the context of chronic pain, there is an increased expression of Nav subtypes 1.5, 1.6, and 1.7. Moreover, Nav subtypes 1.1, 1.2, and 1.8 are also found on keratinocytes. The rapid onset of phenytoin's effects and the absence of detectable blood levels may be explained by its action on both Nav receptors on peripheral nerve endings and those present in keratinocytes (Kopsky et al., 2022).

The lipophilic nature of phenytoin's topical formulation enhances its ability to penetrate the epidermis, leading to a localized blockade of sodium channels (Hesselink, 2018). Previous research has suggested that the mechanism of action of topical phenytoin may involve three key components of skin tissue: small nerve fibers, keratinocytes, and immunocompetent cells. Our findings further corroborate this hypothesis and encourage a reevaluation of therapeutic approaches targeting the skin in the treatment of chronic pain. The skin may also serve as an effective biofeedback system, transmitting inhibitory signals to the central nervous system.(Kopsky et al., 2022).

In addition, there are several other topical anticonvulsants that are used for neuropathic pain therapy and can reduce pain. However, in this study other topical anticonvulsants were not used as much as topical phenytoin, so it is still necessary to know the use of other topical anticonvulsants (Kopsky et al., 2022).

The repositioning of phenytoin as a topical management of neuropathic pain shows a lot of attention, especially because of its non-selective mechanism of action on sodium channels (Hesselink et al, 2018). For the future, further research can be carried out, so that it can compare the effectiveness of phenytoin with other topical anticonvulsants in reducing pain and the right concentration to reduce pain significantly with minimal side effects. Topical analgesics used to treat neuropathic pain are lidocaine patch 5% and capsaicin patch 8%, although the quality of scientific evidence is very low to moderate, and thus proposed as a second-line treatment (Kopsky et al., 2022).

Conclusion and suggestions

Topical phenytoin demonstrates significant potential as a therapy for neuropathic pain, offering an attractive alternative to oral medications, which are often associated with adverse side effects. The use of phenytoin in topical formulations can effectively reduce pain with a rapid onset of action, without producing detectable plasma levels, thereby minimizing the risk of systemic side effects.

The findings of this review study indicate that topical phenytoin not only reduces pain intensity but also improves the quality of life for patients by alleviating allodynia and enhancing sleep quality. However, further research is needed to compare the efficacy of topical phenytoin with other topical anticonvulsants and to explore the optimal concentration that can provide maximum benefits with minimal risks.

The findings of this review study indicate that topical phenytoin not only reduces pain intensity but also improves the quality of life for patients by alleviating allodynia and enhancing sleep quality. However, further research is needed to compare the efficacy of topical phenytoin with other topical anticonvulsants and to explore the optimal concentration that can provide maximum benefits with minimal risks.

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References

Bouhassira, D. (2019). Neuropathic pain: Definition, assessment and epidemiology. *Revue Neurologique, 175*(1–2), 16–25. https://doi.org/10.1016/j.neurol.2018.09.016

Coderre, T. J. (2018). Topical drug therapeutics for neuropathic pain. *Expert Opinion on Pharmacotherapy, 19*(11), 1211–1220. https://doi.org/10.1080/14656566.2018.1501026

Dydyk, A. M., & Conermann, T. (2024). Chronic pain. *In StatPearls*. StatPearls Publishing. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK553030/

Finnerup, N. F., Kuner, R., & Jensen, T. S. (2021). Neuropathic pain: From mechanisms to treatment. *Physiological Reviews, 101*, 259–301. https://doi.org/10.1152/physrev.00045.2019

Gupta, M., & Tripp, J. (2021). Phenytoin. Retrieved from http://europepmc.org/books/NBK551520

Hesselink, J. M. K. (2018). Topical phenytoin in painful diabetic neuropathy: Rationale to select a non-selective sodium channel blocker. *Asclepius Clinical Research in Neurology, 1*(1), 1–5.

Hesselink, J. M. K., Mulder, J. K., & Kopsky, D. J. (2018). Rationale for the repositioning of phenytoin as a topical analgesic for peripheral neuropathic pain and a personalized and investigator-driven development plan. *Annals of Pharmacology and Pharmaceutics, 2*, 144.

Hesselink, J. M. K., & Notermans, N. C. (2018). Topical phenytoin formulations for pain in small fiber neuropathy: A pathogenetic approach. *Annals of Pharmacology and Pharmaceutics, 3*(1), 1–4.

Kocot-Kępska, M., Pawlik, K., Ciapała, K., Makuch, W., Zajączkowska, R., Dobrogowski, J., Przeklasa-Muszyńska, A., & Mika, J. (2023). Phenytoin decreases pain-like behaviors and improves opioid analgesia in a rat model of neuropathic pain. *Brain Sciences, 13*.

Kocot-Kępska, M., Zajączkowska, R., Mika, J., Kopsky, D. J., Wordliczek, J., Dobrogowski, J., & Przeklasa-Muszyńska, A. (2021). Topical treatments and their molecular/cellular mechanisms in patients with peripheral neuropathic pain—Narrative review. *Pharmaceutics, 13*, 450.

Kopsky, D. J., & Keppel Hesselink, J. M. (2018). Single-blind placebo-controlled response test with phenytoin 10% cream in neuropathic pain patients. *Pharmaceuticals, 11*(4), 122. https://doi.org/10.3390/ph11040122

Kopsky, D. J., Keppel Hesselink, J. M., Russell, A. L., & Vrancken, A. F. J. E. (2022). No detectable phenytoin plasma levels after topical phenytoin cream application in chronic pain: Inferences for mechanisms of action. *Journal of Pain Research, 15*, 377–383. https://doi.org/10.2147/JPR.S345347

Kopsky, D. J., Keppel Hesselink, J. M., & Others. (2022). Enriched enrollment randomized double-blind placebo-controlled cross-over trial with phenytoin cream in painful chronic idiopathic axonal polyneuropathy (EPHENE): A study protocol. *Trials, 23*(1). https://doi.org/10.1186/s13063-022-06806-8

Martins, J. P., & Marson, F. A. L. (2024). A narrative review of the complex panorama regarding chronic neuropathic pain mainly for the psychological issues. *Heliyon, 10*(19), e38282. https://doi.org/10.1016/j.heliyon.2024.e38282

Meregalli, C., Monza, L., & Joost, L. M. J. (2022). A mechanistic understanding of the relationship between skin innervation and chemotherapy-induced neuropathic pain. *Frontiers in Pain Research, 3*. https://doi.org/10.3389/fpain.2022.1066069

Mu, A., Weinberg, E., Moulin, D. E., & Clarke, H. (2017). Pharmacologic management of chronic neuropathic pain: Review of the Canadian Pain Society consensus statement. *Canadian Family Physician, 63*(11), 844–852. Retrieved from https://www.cfp.ca/content/63/11/844

Murnion, B. P. (2018). Neuropathic pain: Current definition and review of drug treatment. *Australian Prescriber, 41*, 60–63. https://doi.org/10.18773/austprescr.2018.022

Purba, J. S., & Aninditha, T. (2017). Nyeri neuropatik. In *Buku Ajar Neurologi (Buku 2)* (pp. 593–608).

Raja, S. N., Ringkamp, M., Guan, Y., & Campbell, J. N. (2023). John J. Bonica Award Lecture: Peripheral neuronal hyperexcitability—The "low-hanging" target for safe therapeutic strategies in neuropathic pain. *Pain, 161*(9). https://doi.org/10.1097/j.pain.0000000000000183

Torta, R., Ieraci, V., & Zizzi, F. (2017). A review of the emotional aspects of neuropathic pain: From comorbidity to co-pathogenesis. *Pain Therapy, 6*(Suppl 1), 11–17. https://doi.org/10.1007/s40122-017-0088-z