

## Chronobiology of neuropathic pain and the use of topical phenytoin in painful diabetic neuropathy.

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### Abstract

**Patients suffering from peripheral neuropathic pain frequently report sleep disturbances, and allodynia during the night further contributes to the disturbed sleep. The chronobiological research into neuropathic pain syndromes is virtually absent. We developed a time-contingent chronotherapeutic pain therapy based on the topical application of phenytoin cream. Phenytoin cream can be applied before bedtime and it reduces pain and allodynia within a short timeframe of 20 minutes. Pain is reduced and sleep improves. We will present a case study to illustrate this.**

**Keywords:** Nocturnal, circadian, rhythm, pain, treatment.

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### Introduction

Nocturnal pain and sleep disturbances are frequently reported by patients suffering from painful peripheral neuropathies, such as painful diabetic neuropathy (PDN) [1,2]. From experimental paradigms and patients' own reporting, we know that neuropathic pain is most severe during the evenings and at night. This is supported by findings from animal pharmacology. In sciatic nerve constriction injury models, rats also have a poor quality of sleep and reduced sleep efficiency [3]. Misschien is het beter om het als volgt te formuleren: In 1970/80/90's it was first reported that nerve pain after the stimulation of the nervus suralis led to the highest pain scores in the late evenings and early mornings [4]. Patients reported similar enhanced pain experiences, for instance when suffering from diabetes of herpes zoster pain [5,6]. This is referred to by some authors as the inverse diurnal pattern with pain highest during evening hours [6]. In healthy individuals, disturbed sleep leads to an increased sensitivity to pain [7]. Many of our patients at the institute for neuropathic pain in the Netherlands complain of disturbed sleep, due to burning pain in feet and legs, restless legs and allodynia. Sleep and pain experiences therefore seem intensely related [8]. Apart from the evident relationship between sleep and pain, chronobiological aspects may play a role here. Chronobiology is increasingly recognized as an important factor in health and disease, leading to a new focus of interest, known to be the medical chronobiology [9]. The chronobiology of neuropathic pain is a separate chapter in this field. We will review the current literature and present a case in order to further stipulate the importance of the relationship between sleep and neuropathic pain.

### Medical chronobiology of neuropathic pain

Research on the topic of chronobiology and neuropathic pain is still immature, as only five papers could be identified in PubMed using the combination of key words 'chronobiology' and 'neuropathic pain'. The first paper by Odrceich et al from more than a decade ago, found that the intensity of neuropathic pain progressively increases throughout the day and that this was unaffected by treatment with active pharmaceutical ingredients (APIs) such as gabapentin and/or morphine [5]. The first paper mentioning chronobiology in its title was a review paper

published by Gilron and Ghasemlou [10]. They pointed out that by the 1950's the interrelationships between morning stiffness, nocturnal pain and swelling of the joints were first indicators of the importance of chronobiology in pain syndromes. Based on these findings, the importance of circadian patterns of nociception in osteoarthritis and rheumatoid arthritis was established. Diurnal patterns of pain fluctuation received only little attention in neuropathic conditions. Novel neuropathic pain treatments and time-contingent pain therapy are needed in this field [11,12]. Smolenski et al discussed a great many disorders, including neuropathy, and came to the same conclusion that chronopreventive and chronotherapeutic strategies are needed [13]. In a recent article, the importance between circadian rhythms and the function of the neuroimmune systems in chronic pain states was emphasized [14]. This seems a quite important topic, as mild neuro-inflammatory conditions could play a pathogenic role in various forms of peripheral neuropathic pain, and phenytoin has in addition to its sodium blocking properties an anti-inflammatory mechanism of action [15]. Based on these papers it is clear that original clinical studies in the field of the neurobiology of neuropathic pain are needed.

### *Topical application of phenytoin cream: a new chronotherapeutic strategy*

The findings from researchers indicate that it seems quite important to look for new treatment modalities to reduce pain throughout the day and significantly during the night, so-called chronotherapeutic strategies [5,10]. These are therapies that can be applied before going to bed and during the early hours of the morning after waking up, based on a quick onset of action. We might have developed such a therapy via the topical application of a co-analgesic.

Over the past decade we have developed a number of creams containing co-analgesics such as ketamine, amitriptyline, baclofen, and clonidine [16]. In 2015 we started a new development project based on an old co-analgesic: phenytoin. Phenytoin has all the basic characteristics of a co-analgesic and due to its low molecular weight, its lipophilicity and the fact that it is a broad-acting sodium channel blocker the compound

is suited to be compounded in a cream [17]. We have developed a topical formulation containing 5%, 10%, 15% and 20% phenytoin and believe that this cream can bring fast relief, within 20 minutes, as well as during the night [18].

In a cohort of 70 patients we recently reported that the onset of action for both 5% and 10% phenytoin cream was around 15 minutes after application, while the duration of effect was around 5 hours for the 5% cream and around 9 hours for 10% phenytoin cream [19]. Most of our patients report that after applying the cream before bedtime, they do not wake-up again due to pain. To illustrate this, we will present a short case of a patient reporting a considerable relief of sleep disturbances after the use of topically applied phenytoin 10% cream. Based on this case we suggest that topical phenytoin seems to be a chronotherapeutic strategy.

### Case Presentation

A 63-year-old male patient was diagnosed by the neurologist as suffering from a 'very disabling small fiber neuropathy'. Pregabalin 525 mg daily and oxycodone 10 mg as needed did not reduce the pain sufficiently enough, and the mean pain score on the 11-point NRS was 8-9. We prescribed phenytoin 10% cream, and the amount per application used by the patient was high: one tube of 30 grams of phenytoin 10% cream was used in a 4-5 day period, thus he used 6.7 grams cream daily, corresponding to 670 mg phenytoin applied on the intact skin. For safety purposes, we analyzed the level of phenytoin in the blood, 25 days after application daily of the cream, and the last application before plasma sampling was 2.5 hours in order to measure at the hypothesized T-max time. The plasma level of phenytoin was below the limit of detection. This finding was duplicated in 15 other patients at our clinic, demonstrating that phenytoin has an intradermal mechanism of action and does not act via blood distribution.

The patient reported a fast onset of analgesia; around 10 minutes after application of the cream he reported a clinical relevant reduction of pain of around 60% to 70%. After some months of using the cream the patient reported that pain would reduce approximately 5/10 minutes following application. The pain-reducing effect lasted for nearly a full day, so he rarely applied the cream twice a day. He reported a significant reduction of his sleep disturbances; his sleep quality improved 60/70% and most of the nights he did not reawaken due to pain.

### Discussion

This case demonstrated the value of applied phenytoin cream before sleep, its quick action of onset within 10 minutes after application and the impact of reducing the pain on the sleep quality of this patient. Liu and Wood stated that studying the peripheral nervous system is an important step in developing an understanding of pain mechanisms for identifying new analgesic drug targets [20]. They also indicated that sodium channel blockers targeting sodium channels at the periphery, among them Nav1.7, Nav1.8, and Nav1.9, could potentially reduce the side effect profile of systemic administered analgesics. Clearly, as we pointed out, post-translational modifications on sodium channels occur in diabetes, which are especially relevant for the nociceptors and the small nerve fibers in the skin [21]. Topically

applied phenytoin cream blocks sodium channels, among them Nav1.7, Nav1.8, and Nav1.9, could therefore be of more use than the recently developed highly selective sodium channel blockers that, for instance, only block the Nav1.7 channel [22,23]. In our first case series of patients suffering from PDN among other symptoms, we presented an important fact further supporting the efficacy of phenytoin cream in these patients. The first being that the onset of action is within a 20 minutes' frame, and the second is that the duration of action for 10% phenytoin cream is around twice the duration of action of the tested 5% cream [19]. In some cases of a partial response, higher concentrations up to 30% could even bring more analgesia, around 8 hours [24]. A duration of action of around 8 hours and an expedited onset of action is especially relevant for patients suffering from nocturnal pains [25]. Furthermore, in elderly patients suffering from burning pain, phenytoin cream can be of great use and many of our patients suffering from PDN and secondary sleep disorders complain of such pains [26]. For instance we have seen a patient suffering from PDN, with the pain characteristics of burning, tingling, and pins and needles, all in the same area as the numbness. He scored his pain as 8 on the NRS. The most intense pain was reported at night, with a pain score of 9-10 on the NRS, and the patient was unable to sleep. We prescribed phenytoin 10% cream, applied to both feet: the onset of action was 5 minutes and pain was reduced to an NRS score of 3, while the duration of analgesic effect was 8 hours. After applying the phenytoin 10% cream, he reported that he was able to sleep again and that the pain was considerably less. It therefore seems that phenytoin cream might become a valuable new therapeutic option for patients suffering from PDN, and the cream also helps to improve pain-impaired sleep. We have started the preparation of phase III studies after consultation with the Dutch Medicines Evaluation Board.

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