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# Topical Amitriptyline: Can It Reduce Localized Neuropathic Pain?

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## Abstract

Tricyclic antidepressants (TCAs) such as amitriptyline and doxepin have been explored in topical formulations for the first time in 1981. Since that time, a number of case reports and studies have been published to evaluate the role of TCAs in itch and peripheral neuropathic pain. For the treatment of itchiness, doxepin was more effective compared to a first generation antihistaminic in a topical formulation and more tolerable. Amitriptyline was first formulated as a transdermal formulation, and its percutaneous absorption was established in an animal model. However, it remained unclear whether amitriptyline was supposed to lessen pain via central, peripheral or cutaneous mechanisms. This absence of clarity was never thematized and led to confusing drug development steps. Formulations could not be optimized given this lack of focus. In the absence of adequate animal models and dose-range studies, the biological optimal dose could not be selected and most clinical studies were inconclusive, most probably due to the selection of an insufficient dose. The question whether topically applied amitriptyline can reduce localized peripheral neuropathic pain has therefore never been properly addressed.

**Keywords:** Topiceuticals; Neuropathy; Pain; Treatment; Topicals; TCA; LNP; Phenytoin; Gabapentin

## Introduction

It is clear that there are many advantages for a patient if a topical analgesic formulation is prescribed. However, a topically applied analgesic compound can only result in pain reduction if a number of critical issues are analyzed and solved. It seems that these issues have not been recognized in literature to the full extent, and therefore are not yet totally solved. Three of the main issues are:

1. Mechanism of action of the active pharmaceutical ingredient (API) related to the pathogenesis of the neuropathic pain condition
2. Choice of vehicle
3. Concentration of API

It must be clear that a topical analgesic can only reduce pain if its mechanism of action is targeted to the pathogenetic/pathophysiological cascade which leads to pain. Strangely enough this quite important issue seems to have escaped our attention. It should, however, play a key role in selecting the appropriate patient group to include in clinical studies.

I will discuss these three topics related to the data gathered so far with topical formulations of amitriptyline. One reason for this focus is related to our experience. Amitriptyline cream is used in our clinic, mostly in a high dose, 10% compounded in a topical cream. Most patients suffering from burning pain due to peripheral neuropathic pain for whom we prescribe this cream are quite satisfied, and we rarely see side effects which are mostly transient burning [1].

In the recent Cochrane review on topical analgesics for acute and chronic pain in adults, we can find only one short statement related to amitriptyline: *'Topical use of other drugs such as ketamine and amitriptyline is known; there are few trials, but no systematic reviews'* [2]. However, topical amitriptyline has been used since 1981 and many lines of evidence converge into a relative convincing argumentation that topically applied amitriptyline has value in the treatment of localized neuropathic pain (LNP). In a recent review, it was emphasized that topically applied amitriptyline at concentrations between 2% and 10% has been successfully used in a number of neuropathic pain states, as well as in complex regional pain syndrome (CRPS), multiple sclerosis and vulvodynia [3]. It is therefore of use to explore the context which led to the various case studies and controlled studies of the clinical efficacy of topical amitriptyline in LNP.

### Short history of topical amitriptyline and rationale

In 1981 in an elegant human paradigm based on histamine provoked itch, Bernstein et al were able to demonstrate the anti-pruritus effects of amitriptyline [4]. This led to the application of topical formulations containing tricyclics in pruritus [5]. TCAs seemed even more effective and giving rise to fewer side effects compared to classical antihistaminics in topical formulations such as diphenhydramine [6]. It was clear that in

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1990 the line of thinking was to find formulations of TCAs that led to sufficient transdermal (percutaneous) absorption. The sole argument given was that topical administration of APIs requires little motivation on the part of the patient; it leads to a constant administration of the active compound and bypasses the gastrointestinal tract, thus providing a good alternative of administering drugs to those patients with compliance problems due to tolerability issues [7]. This was also the reason to explore in a mouse model the percutaneous absorption of amitriptyline and imipramine along with their N-demethylated analogs, nortriptyline and desipramine. The concentrations in the blood of these APIs resembled low therapeutic to toxic concentrations in human.

In a review article on antidepressants in neuropathic pain from 2003, the author argued that the peripheral activity of antidepressants suggests that topical application of TCAs may be useful in treating neuropathic pain, and in this context he stressed the findings of the percutaneous absorption of the antidepressants assessed in the above described mouse model [8]. The author herewith implicitly suggested that a transdermal amitriptyline formulation needs to lead to sufficient plasma levels to induce an effect. Indeed, such approach leading to sufficient blood levels of amitriptyline after topical application was already known in the clinic [9]. For nortriptyline, special transdermal formulations have also been developed [10]. The rationale for the use of topically applied analgesics as given by Ness et al. [11] is that they may selectively deliver active ingredients to the peripheral sites of action, and they may be associated with improved absorption and/or improved tolerability of drugs through the avoidance of contact with the gastrointestinal system. This is again in line with former papers, and does suggest transdermal resorption as a primary goal to reach when developing topically.

## Mechanism of action and the pathogenesis of the neuropathic pain condition

Interestingly, it is in one of the first publications (1981) on the pharmacological action of topically applied amitriptyline that we find a clear rationale between topical mechanism of action of amitriptyline and the pathogenesis of itch [3]. Itch and pain have many similarities, and on the level of the skin both are linked to peripheral sensitization of C and A-delta nerve fibers [4]. The 1981 article is a rare and early example of how to proceed intelligently in the field of topical research related to the topic of this chapter. The study evaluated the inhibition of histamine-induced pruritus by topical tricyclic antidepressants, and both the effects of doxepin, amitriptyline hydrochloride and diphenhydramine were assessed in a human double-blind itch evaluation paradigm in 40 volunteers. Solutions of diphenhydramine (5%), doxepin hydrochloride (5%), and amitriptyline hydrochloride (5%) were prepared in an aqueous/alcohol vehicle. These solutions, as well as the vehicle controls, were applied to areas on the flexor-side of forearms of the subjects and allowed to dry subsequently. The itch threshold, provoked by the histamine solution in different solutions, was assessed. The distribution of threshold concentrations of histamine-inducing itch showed a significantly increased frequency of itch thresholds in the vehicle-treated areas compared with the areas treated with all active compounds. The rationale to test amitriptyline in this itch paradigm was directly related to its mechanism of action: the antihistaminic 'side effects' and potent histamine receptor binding capacity of the compound at one hand and the pathogenetic relevance of histamine in itch at the other. The authors noted the major pharmacologic effects of amitriptyline on the re-uptake of serotonin and nor-epinephrine at nerve endings, but this was not though of any relevance for their study, it was the antihistaminic properties that interested them. The selection of doxepin and amitriptyline, both tertiary amine type tricyclics, was based on the fact that they possessed the highest antihistaminic potency ratio of any of this class of compounds.

The authors have addressed the pathogenesis of itch on the skin level and made the rational choice of assessing the effects of amitriptyline as tertiary amine type tricyclic based on its high antihistaminic potency. Such rationale is lacking in most papers on topical analgesics. First, it seems that many authors evaluating topical analgesics randomly cluster together patients who are suffering from a variety of neuropathic pain syndromes. For instance the neuropathic pain that persists after a herpes zoster infection is related to the damage of peripheral and central neurons and is hypothized to be based on byproducts of the immune and inflammatory response triggered by the varicella zoster virus reactivation [13]. On the other hand, chemotherapy-induced peripheral neuropathy (CIPN) is linked to the pathological action of different classes chemotherapeutic agents, resulting for instance in the case of paclitaxel, vincristine, and bortezomib in microtubule depolymerization and disruption of mitotic spindles, causing cell cycle arrest [12]. Furthermore, these compounds result in increased expression of the non-selective cation channels, TRPV1 and TRPA1, and small nerve fiber neuropathy is commonly seen [14,15]. The pathogenesis and pathophysiology of these 2 variants leading to localized neuropathic pain is so different that it seems naive to expect one single analgesic to be active in both varieties, unless the analgesic has a mechanism of action which is common to these two forms. To date, such communality is still unknown. Secondly, some authors introduce analgesics in topical vehicles and oversee the fact that the mechanism of action of those analgesics are only central (as far as we know), such as in the case of the gabapentoids. Thus, a topical administered gabapentin cream, without any known mechanism of action at skin level, can only be active in an adequate transdermal formulation.

In Figure 1 we compare the rationale to administer topical amitriptyline in itch and phenytoin, a broad acting sodium channel blocker in localized neuropathic pain, and compare these rational approaches with the application of gabapentin cream [16]. To date, for the latter there is no target in the skin.

A second aspect of some importance is that in many studies it is unclear whether the authors are focused on intradermal targets

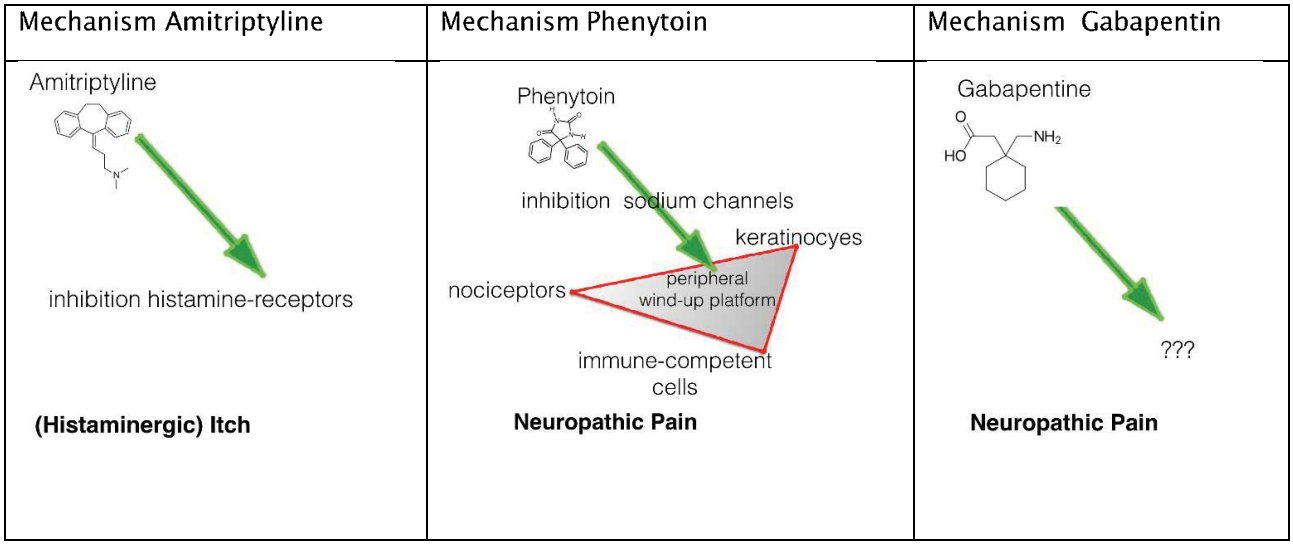


**Figure 1:** The mechanism of action for 3 topical formulations compared: amitriptyline has been formulated for the treatment of itch, phenytoin and gabapentin for peripheral neuropathic pain. For the first two topical formulations a clear rationale exists, for topical gabapentin it is absent as there is no target in the skin. Gabapentin topical formulations therefore can only be formulated as transdermal formulations.

or subdermal targets. Such differences can only be dissected by analyzing plasma samples for concentrations of the active drug. If the active drug can be detected, one would also need to explore whether the plasma level is in the correct range and not in the low, non-active range. We have never come across a paper analyzing such important questions. Hand in hand with this item, the argumentation of the choice of vehicle is often missing or even counter-intuitive as we will see in the next paragraph.

### Choice of vehicle

In the literature, pharmaceutical aspects related to the selected topical formulation with APIs, such as amitriptyline, ketamine and baclofen, are, with only a few exceptions, not described in detail. Even in case of transdermal preparations compounded with a Pluronic Lecithin Organogel (PLO) base, recipes given in literature differ. If we compare such recipes of PLO, we can see that although different approaches lead to a PLO, the procedures to compound these are quite different, and thus the pharmaceutical and physicochemical properties of the gels might also be different, possibly leading to different clinical effects. In all of the studies, there is no thorough line of arguments given to support the choice of the vehicle or the specific way of compounding the cream. In most cases, a PLO base was selected, although such a gel seems to induce patient compliance issues owing to lack of convenience in applying. No studies have ever been published comparing different vehicles. This comparison is also missing in a number of patents in this matter we reviewed. In order to test the efficacy of amitriptyline, one needs to compare the suitability of the selected vehicle in well-designed pilot trials. In Figure 1 we present the relation between topical formulations of 3 compounds and the indications. Amitriptyline for instance has been formulated in the past for the treatment of itch, and phenytoin and gabapentin are formulated for peripheral neuropathic pain. For the first two topical formulations, a clear rationale exists; for topical gabapentin the rationale is absent, as to date there is no target in the skin identified. Gabapentin topical formulations therefore can only be formulated as transdermal formulations. The compounded gabapentin formulations should therefore result in measurable gabapentin plasma levels in the effective range.

### Concentration of compound

It is surprising that a well-conducted dose findings study in this field has never been designed. A number of clinical studies and case studies have been published, evaluating concentrations of amitriptyline between 1% and 10%, and there are some indicators that there could be a dose-response curve, where high concentrations lead to a better efficacy [1]. However, it is not yet clear whether the increased response to a higher concentration is a result of a better effect at the level of the localized targets in the skin, or that it is a result of systemic absorption. Surprisingly, we could not find any study where amitriptyline levels have been monitored in a systematic way after the application of topical amitriptyline.

## Conclusion

Topical formulations of amitriptyline might help to ease pain in neuropathic pain patients, but only if the concentration selected is high enough and the selected vehicle is optimal. In case of transdermal formulations where sufficient blood levels are required, one should systematically analyze plasma levels after application. This has never been properly documented. If one selects a topical, dermal formulation and wants to reach targets in the skin, for instance in cases of burning pain in diabetes or small fiber neuropathy, one needs to select a different formulation [17]. Amitriptyline has clearly a potential as a topical analgesic but to date has never been properly investigated.

## Conflict of Interest

The author is one of the patent holders of two patents related to repurposing of phenytoin in neuropathic pain: 'Topical phenytoin for use in the treatment of peripheral neuropathic pain' and 'Topical pharmaceutical composition containing phenytoin and a (co-) analgesic for the treatment of chronic pain'.

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