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# Thinking Out of the Pillbox: The Relevance to Topiceuticals in the Treatment of Neuropathic Pain

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#### Abstract

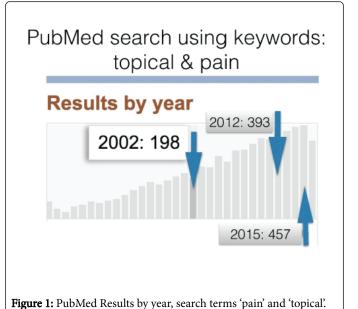
Topiceuticals can be defined as specialized pharmaceutical formulations containing topically applied drugs. Topiceutical analgesics need to be differentiated from transdermal formulations of analgesics. The latter formulations are specially designed for the active pharmaceutical ingredient to penetrate all skin structures and to generate measurable plasma levels of the formulated analgesic, such as in fentanyl plasters and topical NSAIDs. Its mechanism of actions is thus based on the systemic drug-effects and the formulations act merely as controlled release reservoirs. Topiceutical analgesics however are characterized by local analgesic effects in the absence of systemic effects, such as lidocaine and capsaicin plasters. Lidocaine and capsaicin plasters however have a number of drawbacks based on low convenience of use and local side-effects, reducing patient compliance. Topiceutical analgesics based on compounded creams should not cause such compliance issues and might become valuable new treatments for neuropathic pain. Topical compounded creams deserve a place in the modern armamentarium of the pain physician, once certain key issues such as optimal formulation and concentration are solved.

We will discuss some key issues related to Topiceuticals and also present an individualized procedure to quickly differentiate responders from non-responders to topical creams. This procedure might also be helpful to evaluate efficacy and safety in a more practical way compared to full powered randomized placebo controlled trials and might expedite phase II (dose-finding) development.

#### Introduction

Topical analgesics are a new and promising option in pain management. However, many pain specialists still have no insight in their relevance for treating neuropathic pain through use of topical formulations of analgesics such as ketamine, amitriptyline, clonidine or baclofen. These formulations can however contribute significantly in reducing pain once we solve issues related to formulation and concentration. Of course it is as important for topical analgesics to determine the no effect dose and lowest effect dose as it is for new chemical entities (NCEs). Dose-finding however is rare in the development of topical analgesics and often too low dosages are selected, based on restrictions defined by developers or regulatory bodies like the FDA or EMA.

Literature and focus on topical analgesia started to gain some momentum during the last decade of the 20<sup>th</sup> century. The results of a PubMed search using the combined keywords 'topical' and 'pain' made clear that in 10 years' time (between 2002 and 2012) the number of articles covering this topic doubled, from around 200 to circa 400 papers each year (Figure 1); PubMed Results by year, search terms 'pain' and 'topical'. An internet survey from 2002 under physicians resulted in favorable reports of benefit; however, most clinicians at that time perceived the use of such compounded agents to generally be "little or none" [1]. This prejudice has been fueled since by incomplete developments, incorrect dose-ranges tested and suboptimal formulations.



### Think out of the pill box

Some years ago Dr. Pappagello, Clinical Professor of Anesthesiology at the Albert Einstein College of Medicine, Bronx, NY, USA at a plenary session at the EFEC meeting on pain in Florence (2013)

highlighted the relevance of topical analgesia in his lecture 'The age of topiceutcals or Think out of the pill box'. He emphasized that it is extremely important for clinicians to understand the relevance of topical treatments, in terms of efficacy, reduced side-effects and improved tolerability compared to oral analgesics. This however will only happen if we solve certain key issues related to the optimal selection of the formulation and the concentration of the active ingredient of the cream. The rationale to focus on topical analgesics, however, was clearly outlined by his argumentation: 'Why intoxicate patients with systemic drugs', he asked the audience, 'if the problem is regional?' Many patients suffering from regional neuropathic pain are frail and older, and are treated with more than one drug orally. To further add analgesics such as gabapentin, pregabalin and amitriptyline often contributes significantly to the side effect burden of elderly patients, which might already be troublesome. The addition of topically applied analgesics however, to any systemic agent can further improve pain relief without adding to the patient's adverse event burden [2].

## Topiceutical analgesics: Definition and rationale for its application

Topiceuticals are characterized by Galer and Gammaiton as: 'topically applied, locally acting drugs' [2]. Based on this characterization I would like to suggest the following definition for topiceutical analgesics: 'Topiceutical analgesics are special formulations of topically applied and locally acting compounds which reduce pain. These compounds can be classical analgesics or co-analgesics.' It is important to further elaborate on such a definition, because in literature 'topical analgesia' is sometimes used differently. Two examples: with the application of analgesics (for instance for tramadol

and ketamine) on a localized area, such as the tonsillar fossae, one would expect a 'transmucosa' effect [3]. While it would be most logical to measure plasma levels of tramadol and ketamine in such a study in order to quantify buccal resorption, such measurements were not done, and one should have avoided the word 'topical', as the effect was probably not a result of a local action of the drugs in question. The same holds true for many topical NSAIDs, were plasma kinetics clearly indicate systemic effects [4].

It is well known that the pathogenetic root of many neuropathic pain disorders can be found in the skin, due to pathology and hyper excitability of primary afferents and nociceptors. This is the rationale for applying topical formulations of a number of analgesics locally in order to alleviate neuropathic pain at its origin and its source. There are a great number of peripheral nociceptive path mechanisms with play a role in the emergence and intensification of neuropathic pain, mechanisms which can interact with each other and where cross-talk leads to peripheral sensitization. These mechanisms are dependent on the various neuronal and non-neuronal tissue compartments in the skin, such as the small nerve fibers and the nociceptors on one hand and skin resident cells, keratinocytes, and various immune cells, such as the dendritic cells and the mast cells [5].

#### Key issues of development: Formulation and concentration

A number of topical formulations have been developed, or are in development and these formulations can carry classical anesthetics such as bupivacaine, analgesics such as NSAIDs and/or co-analgesics such as baclofen, non-analgesics such as nifedipine, as well as new chemical entities (NCEs). In the (Table 1) below we summarized some active pharmaceutical ingredients (API's) present in topical analgesics.

| Analgesics                      | Co-analgecis                     | Anaesthetics | non-analgesics                               | NCEs; herbals                           |
|---------------------------------|----------------------------------|--------------|--|---|
| NSAIDs (diclofenac, ketoprofen) | TCAs (amitriptyline, imipramine) | lidocaine    | Clonidine                                    | nonivamide                              |
| capsaicin                       | palmitoylethanolamide            | bupvicaine   | Nifedipine                                   | wrightia tinctoria                      |
| menthol                         | gabapentin                       | lidocaine    | Glyceryltrinitrate,<br>Isosorbidi dinitratis |   |
|                                 | ketamine                         | prilocaine   | Clonidine                                    | N,2,3-trimethyl-2-<br>isopropylbutamide |
|                                 | baclofen                         | tetracaine   | loperamide                                   |   |

**Table 1:** Active pharmaceutical ingredients (API's) present in topical analgesics.

For each topical agent various formulations have been proposed and sometimes have been evaluated, for instance for diclofenac there are three topical formulations approved for use in the United States: diclofenac epolamine topical patch 1.3% (DETP), diclofenac sodium 1% gel, and diclofenac sodium topical solution 1.5% [6]. Given the arguments above however, we would not define such formulations as topiceuticals, because NSAIDs are in need of penetrating the skin in order to reach the joint and ligament targets related to the pathogenesis of the pain. It is especially the value of 'real' topiceuticals (without systemic effects) based on the analgesic spectrum of compounds such as gabapentine, ketamine, amitriptyline, clonidine, nifedipine, which I think are in need of more focused development. In a separate article I will further discuss some critical drug development issues, which seem to have led to a suboptimal exploration to date of the value of analgesic topiceuticals, the selection of a correct doserange and the formulation. I will now present a simple tool to select the most optimal dose and/or formulation which may help expediting the development of these therapeutic tools.

# Approach to directly identity responders to topical analgesic therapy and optimize chances for success in dose-finding

We developed a unique system in our institute for neuropathic pain, which I am eager to share with colleagues and which allows us to directly test responders on topical formulations, and to use the feedback of patients to select the best compounded cream for them. The 'best' means the cream that contains the most optimal concentration, or the best vehicle.

We defined this approach as: 'Ex juvantibus topical cream identification based on individualized medicine'. Heterogeneity of response to analgesic therapy is a well-recognized clinical problem. A significant percentage of patients suffering from neuropathic pain appear to be non- or at best partial responders to therapy. Most likely this is due to a mismatch between the therapyused and the pathogenesis of the neuropathic pain in the individual case or of the specific pain disorder.

Based on this insight we explored and developed a special exjuvantibus approach linking diagnosis and therapy-response on an individual patient base: the backbone of individualized medicine. We feel this ex-juvantibus approach helps to more quickly identify the optimal dose for each patient.

In our clinic we created a number of different formulations of various analgesic drugs and tested the various combinations directly, as compounded creams, in the targeted population. Based on our selection of certain base-creams we could create topiceuticals with an action of onset between 10-30 minutes. By using a simple test design (blinded placebo or comparator controlled cross-over testing) we also could, together with the patient, quickly test the pain relief of various formulations and concentrations, compare and select the best. This is the reason why we could optimize our formulations in a fast turnaround time and test for efficacy and safety in each patient individually. By exploring tens of patients with such a response-design one can quickly obtain more information on optimal concentrations and formulations. This led in our clinic to the identification and use of creams based on amitriptyline 5 and 10%, ketamine 10% and baclofen 5% [7-10].

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