

# Phenytoin: Repurposing an Old Molecule and Patent Strategies for Neuropathic Pain

## Abstract

Phenytoin was introduced in the clinic in 1938, and due to its broad mechanism of action it has become a clear prototype of a repurposed or repositioned drug in a variety of indications, from bipolar disorders up to wound healing. Some years ago, we identified phenytoin as a co-analgesic with optimal properties to put into a topical formulation for the treatment of peripheral neuropathic pain. Phenytoin is the archetype of a sodium channel blocking drug and the main target for its efficacy as a neuropathic analgesic resides in the epidemics: the nociceptor. The development however of an old drug in a new off-label indication can only be attractive in case of a well-balanced patent strategy.

## Introduction

Old molecules may have many unexpected promises for the treatment of different disorders, and repurposing or repositioning such drugs is hot. Especially hot, since the clinical development leading to registration for old drugs in principle can be cheap and quick. However, for such development financial incentives are needed, preferably based on a patent strategy.

We started the develop a new topical formulation of an old molecule, phenytoin, in a new indication, peripheral neuropathic pain, and want to share our strategy related to patenting and clinical development of a repurposed drug.

### History of phenytoin as a multi-purpose drug

Phenytoin was first introduced in the clinic in 1938 as a new anti-epileptic, devoid of the side effects of the barbiturates [1]. The compound was never protected by any patent, and thus interest exploring its putative clinical value in many indications was long absent. Since the first use of phenytoin in the neurological clinic, various observations suggested its clinical relevance in a great number of indications, and the driving factor for this repurposing of phenytoin was the Wall Street tycoon Jack Dreyfus (August 28, 1913 - March 27, 2009) [2].

Jack Dreyfus is probably the first non-scientist who can be qualified as a champion for the repurposing of old drugs. In 1963 he took up the courage to ask his treating physician to write him a prescription for phenytoin for his depressed mood. First they believed Dreyfus his remarkable recovery should be attributed to luck, but Dreyfus soon became an ambassador for phenytoin and in a short period of time many others started to benefit from taking phenytoin as an antidepressant, as Dreyfus pointed out at the age of 90 [3].

Phenytoine (diphenylhydantoine; 5,5-diphenylimidazolidine-2,4-dione) was synthesized in 1908 by the German chemist professor Heinrich Biltz [4]. He sold the molecule to Parke-Davis, who had the molecule resting on their shelves for nearly 30 years. After being



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introduced in 1938 in the clinic by the neurologists Merritt and Putnam, one of the key opinion leaders at that time, William Gordon Lennox (1884-1960), expressed great enthusiasm for the new drug: “The big news of the year is the discovery and clinical use of sodium diphenyl hydantoinate (Dilantin Sodium). Merritt and Putnam, working at the Neurological Unit of the Boston City Hospital, report the results of treating 200 non-institutionalized cases of epilepsy” [5].

‘Dilantin sodium’ was subsequently added to the catalog price list of Parke-Davis in June 1938, but was never patented. Phenytoin sodium Extended Capsule, for oral use, was subsequently developed and approved in the USA in 1953. Up to now the listed indication for phenytoin is still the treatment of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery. In 1988 Dreyfus already complained: “today, 50 years after its first use, phenytoin’s only listed indication is still ‘anticonvulsant’. There is a flaw in our system of bringing prescription medicines to the public” [6]. In the same book containing this quotation, ‘The broad range of clinical use of phenytoin’, published in 1988, a great number of indications for phenytoin were listed: aggression, depression, bipolar disorders, wound healing, pain syndromes and tinnitus, among many others.

### Phenytoin as a co-analgesic

Recently we surprisingly found that there is no difference in the amount of evidence to support carbamazepine and phenytoin in the treatment of trigeminal neuralgia [7]. Already as early as 1942, three patients were reported suffering from trigeminal neuralgia; 200-300 mg phenytoin daily was effective in reducing the pain [8]. These data were drivers for us to design a patented strategy around topical phenytoin in the treatment of peripheral neuropathic neuropathic pain syndromes.

Most patents follow the strategy of broadly covering a great number of compounds and derivatives thereof, as well as a wide range of indications. However, patent protection lasts for 20 years, and many compounds and indications remain unexplored after expiry of

the patent, due to the absence of an economic stimulus. Phenytoin is a good example. Although a great number of indications have been explored, clinical development leading to the registration of new indications for this multipurpose drug remain absent. One basically needs patents to make development attractive [9]. In the absence of a patent, not much development work is done, and physicians will always need to prescribe the repurposed drug ‘off-label’, with all its problems.

**Topical phenytoin: its mechanism of action**

In the period 1972-1980 it was established that phenytoin inhibits sodium permeability via its blocking effect on these ion channels [10]. Several studies in the early 1980s described the purification of the sodium channel protein, and initial studies using synaptosomes pointed out that phenytoin blocked voltage-gated sodium channels [11]. To date there is clear consensus that sodium channels are the most important targets of phenytoin [12]. Phenytoin is the archetypical unselective sodium channel blocker [13]. Phenytoin’s binding-site is situated at the inner cytoplasmic membrane, at the inner vestibule of the pore of the ion channel. This most probably explains its broad activity for many if not all of the sodium channels, as this binding site can be found in all members of this channel family [14]. Sodium channels of various types have been characterized on the nociceptors in the skin, the keratinocytes and the immune-competent cells [15]. These 3 elements cross-talk and induce overactive nociceptors, leading to peripheral sensitization (Figure 1). This is exactly the reason why we selected the non-selective, broad acting sodium channel blocker phenytoin in a topical formulation for the treatment of peripheral neuropathic pain. As we have seen recently that a selective NaV1.7 blocker in a topical formulation failed to prove efficacy, this would indirectly support our choice for a broad acting blocker [16].

**Patent and development strategy:** phenytoin in a topical formulation for the treatment of neuropathic pain

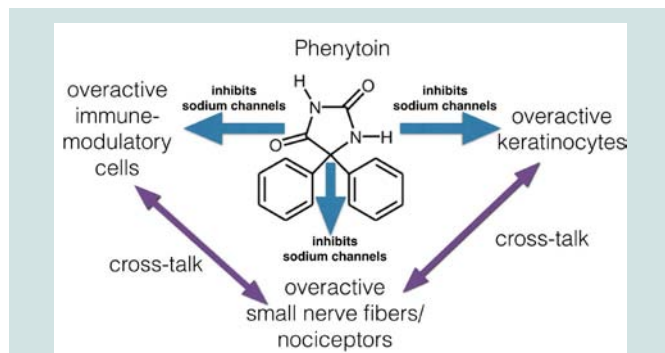
To date we have gathered and published some clinical data, supporting that topical applied phenytoin, in a concentration range of 5-20%, is safe in a number of neuropathic pain syndromes. We also detected and described first indicators for efficacy [17-20]. Based on these data we filed 2 patents on specific topical formulations of phenytoin for the treatment of 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’. Both patents entered the PCT phase earlier this year (2018).

These patents will become cornerstones for a development strategy to change the current situation of off-label use of compounded phenytoin creams. Phenytoin creams are currently prescribed for neuropathic pain, in the Netherlands and the USA, based on our recent findings [16-20]. An investigator driven development plan is under discussion, focused on painful diabetic neuropathy as a first indication. End of phase IIa data, including the proof of concept based on the results of a placebo-controlled single-blind treated cohort of 20 neuropathic pain patients, are available and will soon be published. Consultation with an EU competent authority is planned and we anticipate a quick and lean development up to end of phase III, based on data gathered in the past and published in peer reviewed papers. Especially in the fields of preclinical data and proof of principle, toxicology, side-effects, plasma-levels, pharmacokinetics and mechanism of action we expect to be able to extract sufficient data from the past for supporting the submission related to the registration of a topical formulation in painful diabetic neuropathy. It is our belief that especially the facts that we did not detect any phenytoin plasma levels after administration, and we did not see any serious adverse event in our first 100 patients treated, together with the intra-epidermal mechanism of action, will support an uncomplicated and expedited development.

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**Figure 1:** Phenytoin inhibits sodium channels in intraepidermal components: the nociceptors, the keratinocytes and the immune-competent cells: rationale for developing phenytoin in a topical formulation against peripheral neuropathic pain.

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