

# Recent advances in pharmacological treatment of neuropathic pain

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## Abstract

Recent studies investigating the pharmacological management of neuropathic pain support the efficacy of certain antidepressants, anticonvulsants, and opioids. Novel directions in drug applications include topical applications of patches with either lidocaine or capsaicin and intradermal injections of botulinum toxin. In cases of partial pain relief, drug combinations may be considered.

## Introduction and context

Neuropathic pain is a heterogeneous group of chronic pain conditions caused by lesion or disease of the peripheral or central nervous system [1]. Common neuropathic pain syndromes include painful polyneuropathy (e.g., due to diabetes), postherpetic neuralgia, peripheral nerve injury, radiculopathy, cancer-related pain, and central post-stroke pain. Neuropathic pain often has a negative impact on the mental health and quality of life in these groups of patients. Recommended first-line treatments are the anticonvulsants gabapentin and pregabalin, certain antidepressants (tricyclic antidepressants [TCAs] or serotonin-noradrenaline reuptake inhibitors [SNRIs]), and topical lidocaine [2,3]. Patients may, however, experience no or only partial pain reduction in tolerated doses.

## Recent advances

### **Anticonvulsants and antidepressants**

Different types of neuropathic pain may respond differently to a given drug and there is a need for studies where predictive factors for response are identified. In a recent well-designed randomized controlled trial (RCT), gabapentin in doses up to 2400 mg/day failed to relieve pain in patients with post-traumatic or post-operative nerve injury [4], although the study showed marked improvement on several secondary outcome measures, including pain relief and Patient Global Impression of Change. Also, flexible-dose regimes of pregabalin seem

to provide a better combination of pain relief and few discontinuations than a fixed dose regime [5].

Levetiracetam is a novel anti-epileptic drug that binds to the synaptic vesicle protein SV2A in the brain and spinal cord. Despite the antinociceptive effect found in animal models of neuropathic pain, levetiracetam did not relieve post-mastectomy syndrome and spinal cord injury pain [6,7].

The need for mechanism-based approaches and identification of possible predictors for response is also relevant for sodium channel blockers. Except for the use of sodium channel blockers in trigeminal neuralgia, where they are first-line medication, there is limited evidence for efficacy of drugs like oxcarbazepine, lamotrigine, and the newer anticonvulsant lacosamide [2,8,9] in neuropathic pain. However, despite the lack of an overall effect in large-scale trials, subgroups of patients do seem to respond.

Studies with head-to-head comparisons find only minor differences in efficacy between TCAs and gabapentin/pregabalin [10]. SNRIs are also effective in patients with painful polyneuropathy [11] and can be an alternative to TCAs, in particular in patients with cardiac disorders. Selective serotonin reuptake inhibitors provide a clinically meaningful effect in only few patients [12].

### **Opioids**

Opioids also have a role in the treatment of neuropathic pain. Their efficacy is comparable to that of gabapentin/pregabalin and TCAs [2,13,14], but they are not considered first-line drugs due to side effects, tolerance, uncertain long-term safety and efficacy, and so on.

### **Combination therapy**

In cases of partial but insufficient pain relief by a single drug, combinations are often used. Due to a lack of controlled studies, the rationale for such combination therapy has mainly been based on theory, but is now supported by recent RCTs. The best evidence is for the combination of a TCA or an opioid with gabapentin [15-17]. Such combinations are suggested to improve treatment compared with treatment with each drug alone in maximum tolerated doses.

### **New drug classes**

Topical lidocaine is a safe treatment with no or limited systemic side effects. New evidence from an open-label study suggests that lidocaine patches are useful, not only in postherpetic neuralgia or very localized neuropathic pain but also in painful diabetic neuropathy [18].

Transient receptor TRPV1 agonists and antagonists represent a new class of analgesics [19]. A single application of a high-concentration capsaicin dermal patch produced sustained pain reduction in patients with postherpetic neuralgia [20] and painful HIV-associated sensory polyneuropathy [21], although the long-term effect and the frequency of treatments have not been examined. NGX-4010 (marketed name Qutenza<sup>®</sup>), a cutaneous patch of capsaicin 8%, has been given marketing authorization in Europe. The approved indication is: "treatment of peripheral neuropathic pain in non-diabetic adults". NGX-4010 treatments may be repeated every 90 days.

Botulinum toxin type A (BTX-A) given intradermally is another novel topical treatment approach that has been shown to relieve focal painful neuropathy [22], and painful diabetic polyneuropathy in two RCTs [23]. Patients received multiple intradermal injections once in the affected area and the pain reduction lasted for 12 weeks. Large-scale trials and examination of long-term efficacy are needed to test its value for clinical practice.

A phase 2 RCT found that the neuronal nicotinic acetylcholine receptor agonist ABT-594 significantly reduced pain intensity compared with placebo in patients with painful diabetic neuropathy [24]. Unfortunately, ABT-594 treatment was associated with a high number of intolerable dose-related side effects, but the

study suggests that further development of this drug class may present new therapeutic options.

### **Implications for clinical practice**

The best available evidence and knowledge of side-effect profiles still support the current guidelines of using TCAs (or alternatively SNRIs), gabapentin, and pregabalin as first-line therapy and opioids as second line therapy for neuropathic pain. The side-effect profile for opioids is judged differently by some researchers, which may explain why opioids are considered by some as first-line therapy for certain conditions. In order to minimize side effects, recent advances have led to the development of topical agents, including lidocaine patches, NGX-4010 (high-dose capsaicin), and intradermal BTX-A. There is not abundant evidence for these treatments, but their advantage is that they have no or only minor systemic side effects.

If one drug provides only partial pain relief, a combination with another drug class is recommended – for example, an antidepressant or an opioid in combination with gabapentin or pregabalin, or a combination of a topical agent with an oral drug.

Carbamazepine, oxcarbazepine, lamotrigine, and lacosamide have no primary role in the treatment of neuropathic pain (except for trigeminal neuralgia), but whether we can identify subgroups of patients with specific symptoms or signs who will benefit from these treatments is still to be determined. This emphasizes the need for a mechanism-based approach, where patients are classified based on constellations of symptoms and signs rather than a disease-based classification. Hopefully, this will lead to better patient-oriented treatment. Levetiracetam does not seem to have a role in the treatment of neuropathic pain.

### **Abbreviations**

BTX-A, botulinum toxin type A; RCT, randomized controlled trial; SNRI, serotonin noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant.

### **Competing interests**

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