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## **Pharmacological treatments of neuropathic pain: the latest recommendations**

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## **ABSTRACT**

We provide an up-to-date review of the pharmacological treatment of neuropathic pain with emphasis on the latest evidence-based recommendations for its pharmacological treatment. Drugs proposed as first line include tricyclic antidepressants (particularly amitriptyline), serotonin–norepinephrine reuptake inhibitors (particularly duloxetine), pregabalin and gabapentin. Second line treatments include lidocaine plasters and capsaicin high concentration patches for peripheral neuropathic pain only, and tramadol. Third line treatments include strong opioids and botulinum toxin A (for peripheral neuropathic pain). Perspectives include the development of new compounds and a more personalized therapeutic approach, which is made possible by recent progress in the assessment and understanding of neuropathic pain.

**Keywords:** neuropathic pain; pharmacotherapy; recommendations ; personalized medicine

## 1 Introduction

Neuropathic pain is caused by a direct lesion or disease of the somatosensory system and encompasses a large variety of etiologies including peripheral neuropathies, postherpetic neuralgia, traumatic nerve injury, stroke, spinal cord injury and multiple sclerosis (1). This pain is considered as particularly difficult to treat. Numerous therapeutic recommendations for neuropathic pain have been proposed over the past decade (e.g. 2, 3, 4, 5, 6, 7). The Neuropathic Pain Special Interest group (NeuPSIG) of the International Association for the Study of Pain (IASP) recently published guidelines for the pharmacological treatment of neuropathic pain in 2015 (8) based on a systematic review and meta-analysis of published and unpublished trials, excluding trigeminal neuralgia for which specific guidelines have been published (9). These recommendations included randomized, placebo-controlled, double blind studies of drugs used orally or topically at repeated dosages except for those with long term efficacy after unique application (e.g. capsaicin patches) and used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to rate the quality of evidence and strength of recommendations. In this chapter, we will present the main results of these guidelines, the new drugs in development for the treatment of neuropathic pain and the perspectives of personalized pharmacotherapy.

## 2. Drugs currently recommended in neuropathic pain

### **2.1. Drugs recommended first line (strong evidence for their use based on GRADE)**

Tricyclic antidepressants (TCAs), particularly amitriptyline, and serotonin–norepinephrine reuptake inhibitors (SNRIs), particularly duloxetine, have confirmed

efficacy in various neuropathic pain conditions and are recommended first line (Table 1) (8). TCAs and SNRIs act by inhibiting the reuptake of serotonin and noradrenaline, thereby increasing inhibitory control. TCAs also act on sodium channels, beta2 adrenergic receptors and opioid receptors and have a N-methyl-D-aspartate-receptor (NMDA) antagonist-like and anticholinergic and antihistamine effects (10, 11). Side effects include drowsiness, dizziness, dry mouth, and orthostatic hypotension. TCAs may cause QT prolongation, and an ECG is recommended particularly in the elderly before initiating treatment. Although amitriptyline has been the most often examined, all TCAs have similar effectiveness on neuropathic pain. Secondary amines (nortriptyline, desipramine) have less sedative side effects but are not available in France. Tertiary amines (amitriptyline, imipramine, clomipramine) are not recommended at dosages >75 mg/day in patients above 65 years because of their sedative and anticholinergic effects and risk of falls (12).

The efficacy of pregabalin and gabapentin, including extended release formulations (not available in France), is best established for the treatment of peripheral neuropathic pain, to a lesser extent spinal cord injury pain, although the number of negative trials has increased over the last 5 years (Table 1) (8). Their analgesic effects are mainly related to a decrease in central sensitization through binding to the alpha2-delta subunit of calcium channels (13). An additional effect of pregabalin or gabapentin combined with TCAs or opioids as compared to monotherapy has been reported in several trials (14, 15, 16). However, in a large study with a trial design reflecting clinical practice the efficacy and side effect profile of monotherapy at high dosages (600 mg pregabalin or 120 mg duloxetine) were similar to those of combination therapy at

moderate dosages (300 mg pregabalin and 60 mg duloxetine daily) in patients with diabetic NP not responding to monotherapy at moderate dosages (17). Dizziness and drowsiness are the most common side effects and the doses should be reduced in patients with renal insufficiency.

## **2.2 Drugs recommended as second line (weak evidence for their use based on GRADE)**

Second line treatments include topical agents for peripheral neuropathic pain (Table 1) (8). Lidocaine acts on ectopic neuronal discharges through its sodium channel-blocking properties. The efficacy of lidocaine 5% patches has been assessed in peripheral NP, particularly postherpetic neuralgia, but their therapeutic gain is modest compared with placebo (18, 19). Up to 3 plasters can be applied simultaneously to intact skin for 12 hours per day. Side effects are local with mainly skin irritation.

Capsaicin initially activates transient receptor potential vanilloid 1 (TRPV1) ligand-gated channels on nociceptive fibers leading to TRPV1 desensitization and defunctionalization of epidermal nerve fibers (20). The sustained efficacy (up to 3 months) of a single application of high-concentration capsaicin patch (8%) has been reported in diabetic and non-diabetic painful neuropathies and this treatment may be cost-effective compared to pregabalin (20). Capsaicin patches have to be applied by a healthcare provider. Up to four patches can be used at the same time and remain applied for 30-60 minutes. There is minimal systemic absorption and the side effects during application are mainly transient skin reactions with redness, pain, and itching. The treatment may provide up to three months pain reduction after which the treatment can be repeated. The long-term safety of repeated applications seems favorable based

on open prospective studies, but there are no long-term data on the effects on epidermal nerve fibers in patients (8).

Tramadol is a weak opioid with serotonin and norepinephrine reuptake inhibition, which has been found beneficial mainly in peripheral neuropathic pain (Table 1). This drug is recommended as second line mainly because of potential risk of abuse (although less than with strong opioids) and risk of confusion and somnolence particularly in the elderly (8). Tramadol should be used with caution in association with antidepressants (8).

### **2.3. Drugs recommended third line (weak evidence based on GRADE)**

Strong opioids, particularly oxycodone and morphine, are moderately effective in peripheral neuropathic pain, and there is concern about the increase in prescription opioid-associated overdose diversion, misuse and morbidity (22). Therefore these drugs are recommended as third line (Table 1) (8).

Botulinum toxin type A (BTX-A), a potent neurotoxin commonly used for the treatment of focal muscle hyperactivity, has shown efficacy for up to three months after a single set of injections, possibly through a central effect (Table 1). A recent larger-scale trial has confirmed the efficacy of repeated administrations over six months, with enhanced effects of the second injection (23). Botulinum toxin type A is administered subcutaneously in doses of 100-300 IU divided over the area of pain in a specialist setting. The application is painful, and local anesthetics and inhalation of 50% nitrous oxide and oxygen can be used before and throughout the treatment to minimize the pain (23). Besides the pain upon application, the treatment is generally considered safe

although there is limited evidence from long-term studies. Botulinum toxin A should be used by specialists as last choice in refractory cases for peripheral neuropathic pain and limited area of pain (8).

### 3. Drugs with inconsistent results or lack of efficacy

The evidence for efficacy of tapentadol, a mu opioid agonist acting on descending modulation, is weak in peripheral NP, although positive results have been reported in low back pain with a neuropathic component (24). Tapentadol seems to be better tolerated than oxycodone. Studies of antiepileptics other than alpha2delta ligands (e.g. topiramate, oxcarbazepine, carbamazepine, valproate, lacosamide, levetiracetam) have reported negative, weak or inconsistent results, although drugs such as oxcarbazepine are probably effective in subgroups of patients (25) (see “personalized pharmacotherapy”). Oromucosal cannabinoids (2.7 mg delta-9-tetrahydrocannabinol/2.5 mg cannabidiol) have been found variably effective, particularly in multiple sclerosis–associated pain, but several unpublished trials were negative on the primary outcome. Results for selective serotonin reuptake inhibitors (SSRIs), N-methyl-D-aspartate (NMDA) antagonists, mexiletine and topical clonidine have generally been inconsistent or negative (8).

### 4. New drugs in clinical development

A few drugs targeting novel mechanisms of action are under clinical development for the treatment of peripheral neuropathic pain (26). These include in particular subtype selective sodium blocking agents particularly Nav1.7 antagonists (27), EMA 401, a



novel angiotensin type II antagonist effective in a phase II clinical trial in postherpetic neuralgia (28), TPRV1 antagonist and nerve growth factor antagonists (26).

## 5. Towards personalized pharmacotherapy

Treatment of neuropathic pain is currently a “trial-and-error” process. It has been suggested for many years that a mechanism-based classification of pain will improve the treatment of the individual patient (1). One approach is to classify patients based on pain phenotypes (specific symptoms and signs or their combination) with the assumption that the latter reflect specific underlying pain mechanisms (29-35). There is, however, still limited evidence for this approach from well-conducted prospective studies. A phenotype-stratified study used quantitative sensory testing to classify patients into those with and without the “irritable nociceptor” phenotype and the primary outcome was to examine whether there was a better effect of the sodium channel blocker oxcarbazepine on this phenotype (25). This phenotype was defined by the presence of hypersensitivity to thermal or mechanical stimuli and preserved small-fiber function (normal cold and warm sensory thresholds). The study found that oxcarbazepine was more effective in patients with this phenotype. Another trial tested whether the presence or severity of allodynia and sensory deficits as secondary outcomes were predictive of the treatment response to botulinum toxin A (23). This study found that patients with allodynia had better effect of the treatment and that less thermal deficits were associated with greater efficacy of botulinum toxin A. To obtain further knowledge of predictors of drug response, future clinical trials should obtain a detailed description of the individual patient’s pain, including pain descriptors, sensory

signs, and psychosocial factors, and report whether any of these are related to the effect. This could generate hypotheses to be tested in future trials and further analysed in systematic reviews and meta-analyses.

## 6. Conclusions

Evidence based recommendations have recently been updated for the pharmacotherapy of neuropathic pain. Recent progress in the diagnosis, assessment, and understanding of its mechanisms offers the perspective of a more rational therapeutic management, which should result in better therapeutic outcome.

## Disclosure

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**Table 1** Recommended pharmacotherapy for neuropathic pain.

Drug	Mechanism of action	NNT for 50 % pain relief and 95 % confidence interval <sup>1</sup>	Adverse effects	Precautions, contraindications
<i>Antidepressants</i>				
Amitriptyline, Clomipramine Imipramine Nortriptyline <sup>2</sup> , Desipramine <sup>2</sup> ,	Monoamine reuptake inhibition; Sodium channel blockade; Anticholinergic effects	3.6 (3.0-4.4)	Somnolence, anticholinergic effects and weight gain	Cardiac disease, glaucoma, prostatic adenoma, seizure; High doses should be avoided in adults older than 65 years of age
Duloxetine Venlafaxine	Serotonin and norepinephrine reuptake inhibition	6.4 (5.2-8.4)	Nausea, abdominal pain and constipation, hypertension at high dosages for venlafaxine	Hepatic disorder (duloxetine) Hypertension Cardiac disease Use of tramadol
<i>Antiepileptics</i>				
Gabapentin Gabapentin extended-release (ER)/enacarbil <sup>2</sup> Pregabalin	Act on $\alpha_2\text{-}\delta$ subunit of voltage-gated calcium channels, which decreases central sensitization	6.3 (5.0-8.4) for gabapentin 8.3 (6.2-13) for gabapentin ER/enacarbil 7.7 (6.5-9.4) for pregabalin	Sedation, dizziness, peripheral edema and weight gain	Reduce dose in renal insufficiency
<i>Topical agents</i>				
Lidocaine 5% plasters	Sodium channel blockade	NA	Local erythema, itching and rash	None
Capsaicin high concentration patches (8 %)	Transient receptor potential vanilloid type 1 agonist (TRPV1)	10.6 (7.4-19)	Pain, erythema, itching; Rare cases of high blood pressure (initial increase in pain)	No overall impairment of sensory evaluation after repeated applications, caution in progressive neuropathy

<i>Opioids</i>				
Tramadol	Mu receptor agonist; Monoamine reuptake inhibition	4.7 (3.6-6.7)	Nausea, vomiting, constipation, dizziness and somnolence	History of substance abuse, suicide risk, use of antidepressant in elderly patients
Strong opioids (e.g. morphine, oxycodone, methadone)	Mu receptor agonist; Oxycodone may also cause kappa receptor antagonism	4.3 (3.4-5.8)	Nausea, vomiting, constipation, dizziness and somnolence	History of substance abuse, suicide risk, risk of misuse on long-term use
<i>Neurotoxins</i>				
Botulinum toxin type A	Acetylcholine release inhibitor and neuromuscular blocking agent Potential effects on mechano- transduction and central effects in neuropathic pain	1.9 (1.5-2.4) <sup>3</sup>	Pain at injection site	Known hypersensitivity and infection of the painful area

Adapted from refs. [1, 8, 10]

<sup>1</sup> The Number Needed to Treat (NNT) for 50 % pain relief in placebo controlled trials represents the number of patients needed to treat for one to have significant pain relief as compared to placebo). The higher the NNT the lower the proportion of responders compared to placebo (8).

<sup>2</sup> Not available in France

<sup>3</sup> This number comes from small low to moderate quality clinical trials and may have been overestimated. One unpublished clinical trial was negative (NNT unknown) and the NNT in a clinical trial posterior to the meta-analysis was 7.3 (95% CI -3.0-16.6) (23)