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## **French guidelines for neuropathic pain: an update and commentary**

Xavier Moisset<sup>1</sup>, Didier Bouhassira<sup>2</sup>, Nadine Attal<sup>2</sup>

1- Université Clermont Auvergne, CHU de Clermont-Ferrand, Inserm, Neuro-Dol, F-63000 Clermont-Ferrand, France.

2- Inserm U987, APHP, CHU Ambroise Paré hospital, UVSQ, Paris-Saclay University, Boulogne-Billancourt F-92100, France.

### **Corresponding author:**

Xavier MOISSET

Service de Neurologie, CHU Gabriel Montpied

58 rue Montalembert, F-63000 Clermont-Ferrand – France

E-mail: xavier.moisset@gmail.com

Tel: +33 4 73 75 22 01 – Fax: +33 4 73 75 22 02

**Key words:** Neuropathic pain; real-life; trajectories; predictive factors

### **Conflict of Interest Statement:**

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## **Abstract**

Neuropathic pain remains a significant unmet need. French recommendations have been updated in 2020. The goal of this minireview is to provide an update on these published guidelines. Despite newer relevant studies, our proposed algorithm remains relevant. First-line treatments include SNRIs (duloxetine and venlafaxine), gabapentin and tricyclic antidepressants, topical lidocaine and transcutaneous electrical nerve stimulation being specifically proposed for focal peripheral neuropathic pain. Second-line treatments include pregabalin (such position being confirmed by newer studies), tramadol, combinations and psychotherapy as add on, high-concentration capsaicin patches and botulinum toxin A being proposed specifically for focal peripheral neuropathic pain. Third-line treatments include high-frequency rTMS of the motor cortex, spinal cord stimulation and strong opioids (in the lack of alternative). Disseminating these recommendations and ensuring that they are well accepted by French practitioners will be necessary to optimize neuropathic pain management in real life.

## **Keywords**

Neuropathic pain; Neurostimulation; Pharmacotherapy; Psychotherapy; Recommendations; Surgery.

## **Abbreviations**

CBT: cognitive behavioural therapy

DLPFC: dorsolateral prefrontal cortex

M1: primary motor cortex

MCS: motor cortex stimulation

RCTs: randomized controlled trials

rTMS: repetitive transcranial magnetic stimulation

tDCS: transcranial direct current stimulation

TENS: Transcutaneous electrical nerve stimulation

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## 1. Introduction

Diagnostic algorithms and specific tools for neuropathic pain screening and measurement have been developed over the last 20 years, allowing improvement in epidemiological studies [1]. To date, we know that neuropathic pain concerns 7 to 10% of adults in the general population [2]. Electrophysiological approaches can be helpful in the diagnosis of such pain [3] and functional imaging has brought additional information to our understanding of pain/analgesic processes [4]. In 2015, a systematic review and meta-analysis had been published and international guidelines for pharmacological treatment had been proposed [5,6]. However, pharmacology is not the only way to treat pain and other techniques, especially neuromodulation ones were known to be of interest [7,8]. Thus, it was decided to propose French recommendations for neuropathic pain treatment [9,10], encompassing all available approaches.

Those recommendations have been finalized in 2019 and published in April 2020. Based on the GRADE system, recommendations and proposal as a first-line treatment was proposed for serotonin-noradrenaline reuptake inhibitors (duloxetine and venlafaxine), gabapentin and tricyclic antidepressants and, for topical lidocaine and transcutaneous electrical nerve stimulation specifically for peripheral neuropathic pain; a weak recommendation for use and proposal as a second-line treatment for pregabalin, tramadol, combination therapy (antidepressant combined with gabapentinoids), and for high-concentration capsaicin patches and botulinum toxin A specifically for focal peripheral neuropathic pain; a weak recommendation for use and proposal as a third-line treatment for high-frequency repetitive transcranial magnetic stimulation (rTMS) of the primary motor cortex (M1), spinal cord stimulation (for failed back surgery syndrome and painful diabetic polyneuropathy) and strong opioids (in the absence of an alternative). Psychotherapy (cognitive behavioral therapy and mindfulness) was recommended as a second-line therapy, as an add-on to other therapies.

Importantly, several relevant publications have appeared since our guidelines. Hence the aim of the present minireview is to discuss whether these might have an impact on our recommendations.

## **2. Pharmacological treatments**

One of the main changes proposed in our guidelines compared to prior recommendations was the down-grading of pregabalin to second line. A recent meta-analysis confirmed the limited efficacy of this treatment in recent randomized controlled trials (RCTs) [11]. In a Bayesian adaptive, open-label randomized clinical comparative effectiveness study, nortriptyline and duloxetine outperformed pregabalin when pain reduction and undesirable adverse effects were combined to a single end point for the treatment of chronic neuropathic pain [12]. In addition, the risk of misuse is also a major problem with pregabalin [13,14] and this drug is currently the most frequent cause of forged or falsified prescription [15]. Consequently, since May 24, 2021, it has become required to prescribe pregabalin on secured prescriptions in France and prescription has to be renewed at least once every 6 months.

Tricyclic antidepressants are an established treatment for neuropathic pain for years, and experimental data had suggested that they may work through a  $\beta_2$ -agonist action. A recent study confirmed their efficacy [16]. However, it has been found that the  $\beta_2$ -agonist terbutaline had no effect in painful polyneuropathy, suggesting that  $\beta_2$ -agonism seems not to be an important mechanism of action of tricyclic antidepressants in neuropathic pain [16].

Concerning strong opioids, it is clearly noted in the French guidelines that they should be used only as third line if all other options have failed and after careful screening for misuse risk. Recent data obtained in a real-life setting using propensity score matching highlight that as low as 14% of patients treated with opioids for chronic neuropathic pain have a significant

pain reduction [17]. Such data reinforces the fact that strong opioids should be proposed for a very limited proportion of patients. Their prescription is scheduled to 28 days due to misuse risks. For the same safety reasons, the prescription of tramadol has also been reduced to 12 weeks since April 15, 2020.

The experimentation with medical cannabis has just started in France, with the first patient included in March 26, 2021. Overall, 3,000 patients should be enrolled, including 700 patients with chronic refractory neuropathic pain. A systematic review and meta-analysis of pre-clinical studies of cannabinoids has recently shown that selective CB1, CB2, non-selective cannabinoid receptor agonists (including delta-9-tetrahydrocannabinol, THC) and cannabidiol (CBD) significantly attenuated pain-associated behaviors in models of neuropathy [18]. However, the level of evidence for the use of cannabinoid for neuropathic pain treatment remains limited.

Concerning potential new drugs, several of them are under development but none have been approved in France during the last year. Mirogabalin, a new gabapentinoid, is already approved in Japan since 2019 and its development is still ongoing [19]. Several other new drugs such as TGF- $\alpha$ /epiregulin monoclonal antibody named LY3016859 (NCT04476108), P2X3 receptor antagonist such as BAY 1817080 (NCT04641273), and oral NMDA receptor modulator such as NYX-2925 (NCT04146896) are currently under development with ongoing randomized controlled trials. LX9211, a new small-molecule AP2-associated kinase 1 inhibitor with preclinical effectiveness in pain relief, was safe and well tolerated in phase 1 studies [20]. Phase 2 studies are ongoing in both diabetic peripheral neuropathic pain and postherpetic neuralgia.

There was a great hope in the development of a highly selective angiotensin II type 2 receptor antagonist (EMA401). Two phase 2b studies (EMPHENE in patients with postherpetic neuralgia and EMPADINE in patients with painful diabetic neuropathy) were prematurely

terminated due to preclinical hepatotoxicity on long-term dosing [21]. Out of the planned participants, a total of 129/360 (EMPHENE) and 137/400 (EMPADINE) participants were enrolled. The reduction in pain score was numerically in favor of EMA401 arm in both studies with a treatment difference around -0.6 compared to placebo at the end of Week 12. However, as the studies were terminated prematurely, no firm conclusion could be drawn but the consistent clinical improvement in pain intensity reduction across these two studies in two different populations is worth noting.

### **3. Neurostimulation, multimodal approaches and psychotherapy**

One of the originalities of the 2020 French guidelines was to combine pharmacological and other medical treatments including neurostimulation and psychotherapy in a single algorithm. Several high-quality studies have been published regarding the efficacy and safety of rTMS since our recommendations. First, the suspected dose-response for repetitive transcranial magnetic stimulation efficacy has been confirmed in a study comparing various frequencies (5 or 10Hz) and number of pulses (500 or 2000) of M1-rTMS for neuropathic pain [22]. In this study, the best analgesic effect was obtained using 2000 pulses delivered with 10Hz frequency, in accordance with our guidelines. Second, another study provided strong evidence that 3 weeks spaced high-frequency rTMS of M1 resulted in sustained analgesic effect in patients with central pain [23]. This study showed that it is not necessary to perform an “induction” phase with daily rTMS session to obtain a long-term positive effect. This result is of importance for clinical practice as doing 3 weeks spaced sessions is easier than daily sessions in clinical care setting. Finally, a multicenter study has recently compared the 25 weeks analgesic efficacy of M1 or dorsolateral prefrontal cortex (DLPFC) 10Hz rTMS in 149 patients with peripheral neuropathic pain. Contrary to prior studies, this study ensured a real



double blinding since rTMS was conducted using a bifacial coil which active or placebo face was determined by an USB key. Furthermore, the target was controlled using robotic assisted neuronavigation. Results showed that M1 stimulation was effective over 25 weeks with a total of 15 stimulations while DLPFC stimulation was not different from placebo stimulation [24]. Although several mechanisms of action of rTMS have been hypothesized [25], more research on this topic is still necessary and additional analyses need to assess potential predictors of the response. Furthermore, rTMS seems to predict a positive response to epidural motor cortex stimulation (MCS) [26]. However, contrary to rTMS somatotopic effect of MCS have recently been indicated based on a case controlled study [27]. Efficacy of MCS has been confirmed in a recent well-conducted study [28].

Another neuromodulation technique of major interest for some refractory neuropathic pain conditions is spinal cord stimulation. Newer stimulation paradigms using very high frequency (10 KHz) now appear highly effective and have the advantage of being free of paresthesia [29–31]. Regarding the potential relevance of a screening trial before permanent implantation, a recent study showed that although it may have diagnostic utility, there was no evidence that a screening trial strategy provided superior patient outcomes or was cost-effective compared to a no trial screening approach [32]. More evidence will probably be available in the near future to optimize the type of electrodes used and the type of stimulation protocols.

Our guidelines have also outlined the advantage of multimodal approach for neuropathic pain. Interestingly a recent RCT combining transcranial direct current stimulation (tDCS) with mirror therapy showed that it resulted in higher pain reduction than mirror therapy alone in phantom limb pain [33]. Validation of the best combination has still to be investigated.

Lastly, psychotherapy was also considered in our recommendations and we recommend it for neuropathic pain treatment, particularly cognitive behavioural therapy (CBT) and

mindfulness. Interestingly a recent study showed that CBT was more effective than education in patients with chronic pain, emphasizing the relevance of this approach [34].

#### **4. Conclusion**

The current 2020 French recommendations for neuropathic pain treatment remain still relevant and newer clinical studies have even reinforced the level of evidence of several recommended therapies, such as high-frequency rTMS. It is now important to largely disseminate these recommendations and ensure that they are well accepted by French practitioners to optimize neuropathic pain care in clinical practice.

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