

# A review of Neuropathic Pain: From Guidelines to Clinical Practice

Giorgio Cruccu · Andrea Truini

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## ABSTRACT

Neuropathic pain is a chronic condition representing a significant burden for patients, society, and healthcare systems. The prevalence of neuropathic pain in the general population has been estimated at 7–8% and is expected to increase in the future. Neuropathic pain differs from nociceptive pain and requires a different therapeutic approach; and the management of neuropathic pain is complicated and challenging. This chapter discusses clinical practice guidelines for neuropathic pain and their usefulness in clinical practice. **Funding:** Pfizer, Italy.

**Keywords:** Analgesia; Diagnosis; Guidelines; Neuropathic pain; Quality of life; Treatment

## INTRODUCTION

The prevalence of neuropathic pain in the general population has been estimated at

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G. Cruccu (✉) · A. Truini  
Department of Neurology and Psychiatry, Sapienza  
University of Rome, Rome, Italy  
e-mail: giorgio.cruccu@uniroma1.it

A. Truini  
e-mail: andrea.truini@uniroma1.it

6.9–10.0% [1]. A number of factors, including the aging population, increasing obesity rates, and increased survival of cancer patients being treated with interventions likely to cause neuropathic pain, mean that the prevalence of neuropathic pain is likely to increase in the future [2]. Neuropathic pain is a chronic condition which represents a significant burden for patients, society and healthcare systems [3]. Since neuropathic pain is different from nociceptive pain and requires a different therapeutic approach, the management of neuropathic pain is complicated and continues to be a challenge [4].

This chapter discusses the available clinical practice guidelines for neuropathic pain and their usefulness in the clinical practice setting.

## Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

## CLINICAL PRACTICE GUIDELINES FOR THE TREATMENT OF NEUROPATHIC PAIN

In order to facilitate the assessment and treatment of neuropathic pain, clinical practice

guidelines have been published by a number of international and regional professional associations, including the International Association for the Study of Pain [4–6], the European Federation of Neurological Societies (EFNS) [7–9], the National Institute for Health and Care Excellence (NICE) of the UK [10] and the Canadian Pain Society (CPS) [2, 11].

There is a broad agreement among the guidelines on pharmacological treatment of neuropathic pain (Table 1) [12]. Three drug classes have received strong recommendations for first-line therapy in all guidelines: tricyclic antidepressants, particularly amitriptyline; the serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine; and the calcium channel alpha-2-delta ligands gabapentin and pregabalin.

Tramadol, a weak opioid and an SNRI, is recommended by most guidelines for second-line treatment of neuropathic pain. The guidelines produced by NICE recommend tramadol only for use in rescue therapy on the grounds that it was generally associated with higher rates of withdrawal due to adverse events compared with other treatments and that the clinical studies that investigated its efficacy included small numbers of patients and had observation periods of up to 4 weeks [10].

Drugs recommended for third- and fourth-line treatment commonly include strong opioids, anti-epileptic agents other than gabapentinoids, and cannabinoids. Carbamazepine is generally recognized as an effective treatment for trigeminal neuralgia. Topical preparations of capsaicin and lidocaine are recommended for localized neuropathic pain.

## THE USEFULNESS AND LIMITATIONS OF CLINICAL PRACTICE GUIDELINES

There are a number of factors that limit the applicability and usefulness of clinical practice guidelines in the real-world setting. Neuropathic pain is not a single disease, but instead a syndrome that can be caused by a number of diverse etiologies [8], and its clinical manifestations vary significantly [13]. It is therefore

critical to diagnose neuropathic pain correctly; however a widely agreed diagnostic test is still lacking [14].

The EFNS and NeuPSIG guidelines for diagnosis and assessment of neuropathic pain rely on the definition issued by the International Association for the study of pain (<https://www.iasp-pain.org/Taxonomy>), which states that neuropathic pain is that “...caused by a lesion or disease of the somatosensory nervous system”. This definition requires identification of the underlying lesion or disease. Generally, this is not an issue as, the lesion or disease is revealed in the course of clinical examination or from the patient’s account of their medical history. However, in patients who present with pain as the main or even the only symptom, the application of this definition may prevent accurate diagnosis of neuropathic pain [15].

Another limitation regarding the applicability of clinical practice guidelines concerns the classification of neuropathic pain, which, in turn, affects the choice of most appropriate treatment. Traditionally, neuropathic pain has been classified on the basis of etiology, and the EFNS guidelines still adhere to this approach [7]. However, it has been suggested that a classification based on the underlying pathophysiological mechanism might be more effective [16, 17]. In a cross-sectional study of 2100 patients with painful diabetic neuropathy and post-herpetic neuralgia, hierarchical cluster analysis was used to analyze patterns of sensory symptoms [18]. Following this analysis, five distinct symptom profiles that occurred in significant numbers in both patient populations were identified, although their frequencies varied [18]. Another study including 482 patients with neuropathic pain that evaluated the associations between positive neurological symptoms and etiology, type of lesion and pain localization found that, with the exception of idiopathic trigeminal neuralgia and post-herpetic neuralgia, there were more similarities than differences in symptom profiles between various types of neuropathic pain [19]. Both of these studies concluded that a classification based on the type of symptoms or “pain dimensions” was more appropriate than one based on etiology [18, 19].

**Table 1** Summary of recommendations for pharmacological management of neuropathic pain

	EFNS [7]			NICE [10]			CPS [2]		NeuPSIG [4]
	Diabetic neuropathy	Post-herpetic neuralgia	Trigeminal neuralgia	Central neuropathic pain	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain	Trigeminal neuralgia	All neuropathic pain
First-line therapy	Duloxetine Gabapentin Pregabalin TCA Venlafaxine <sup>d</sup>	Gabapentin Pregabalin TCA Lidocaine plasters <sup>a</sup>	Carbamazepine Oxcarbazepine	Gabapentin Pregabalin TCA	Amitriptyline Duloxetine Gabapentin Pregabalin Capsaicin cream <sup>b</sup> (localized pain in patients who wish to avoid or who cannot tolerate oral treatments)	Carbamazepine	Gabapentin Pregabalin Duloxetine Venlafaxine <sup>d</sup> TCA	Carbamazepine	Gabapentin Gabapentin ER/ enacarbil Pregabalin Duloxetine Venlafaxine <sup>d</sup> TCAs
Second-line therapy	Tramadol	Strong opioids Capsaicin cream		Tramadol Strong opioids	One of the remaining 3 oral drugs of the First-line therapy		Tramadol Strong opioids Lidocaine cream <sup>c</sup> Lidocaine patches <sup>e</sup>		Capsaicin patches <sup>b</sup> Lidocaine patches <sup>b</sup> Tramadol

Table 1 continued

		EFNS [7]			NICE [10]		CPS [2]		NeuPSIG [4]
		Diabetic neuropathy	Post-herpetic neuralgia	Trigeminal neuralgia	Central neuropathic pain	All neuropathic pain	All neuropathic pain	All neuropathic pain	All neuropathic pain
Third-line therapy	Strong opioids				Strong opioids	One of the remaining 3 oral drugs of the First-line therapy	Cannabinoids		Botulinum toxin type A
Fourth-line therapy					Lamotrigine (in central post-stroke pain) Cannabinoids (in multiple sclerosis)		Other opioids Lacosamide Lamotrigine Botulinum toxin Lidocaine cream Lidocaine patches	Strong opioids	

CPS Canadian Pain Society, EFNS European Federation of Neurological Societies, ER extended release, NeuPSIG Neuropathic Pain Special Interest Group, NICE National Institute for Health and Care Excellence

<sup>a</sup> For use in the elderly; <sup>b</sup> for use in localized pain; <sup>c</sup> for use in post-herpetic neuralgia; <sup>d</sup> in most European countries, including Italy; venlafaxine is not approved for the indication of “neuropathic pain”, and therefore any such use should be considered off-label

The quality of guidelines for the treatment of neuropathic pain has been evaluated using the Appraisal of Guidelines Research and Evaluation II (AGREE-II) instrument, which consists of five domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability and editorial independence [12]. The lowest scores received by all guidelines were in the applicability domain, with NICE, EFNS, and CPS guidelines for pharmacotherapy having scores of 42, 14, and 0%, respectively; assessment-related guidelines from EFNS and NeuPSIG had applicability scores of 14 and 0%, respectively. Clinical practice guidelines for interventional management published by EFNS, CPS, and NeuPSIG all received 0% for applicability. In this analysis, the rigor of development domain was considered to be most indicative of the quality of clinical practice guidelines [12]. In this domain, the scores for NICE, CPS, and EFSN guidelines for pharmacological treatment were 86, 55, and 55%, respectively [12].

The latest guidelines produced by NeuPSIG for pharmacological treatment were not evaluated in the analysis by Deng and colleagues [12], but these guidelines represent the state-of-the-art in this field and are distinguished from other similar publications in a number of ways [20]. Firstly, these recommendations are based on a meta-analysis of clinical studies of neuropathic pain conducted since 1966, including unpublished trials [4]. Inclusion of unpublished trials allowed for analysis of publication bias to be carried out, which showed that the overall efficacy of drug treatments has been overstated by 10%, with high-concentration capsaicin patches being the most affected [4]. Secondly, in these guidelines, neuropathic pain is treated as a specific entity due to the fact that, generally, the efficacy of systemic treatments does not appear to be affected by etiology [4]. Evidence suggests that HIV-related polyneuropathy and radiculopathy are more refractory to pharmacotherapy compared with other types of neuropathic pain and represent exceptions to this approach [4]. Lastly, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess

the quality of evidence, and recommendations comply with AGREE II guidelines [4].

### How to Select First-Line Treatment

International guidelines rely on randomized controlled trials and provide recommendations on the different drug classes. Nevertheless, in daily clinical practice physicians must choose the specific drug and consider specific issues related to that drug and their patient. The possible choices within the first-line drugs serve to illustrate this issue.

Although pregabalin and gabapentin have the same mechanism of action on the  $\alpha_2\delta$  subunit of the presynaptic calcium channel [21], and randomized controlled trials showed that the two drugs have the same efficacy, pregabalin has a linear pharmacokinetic profile, more favorable than gabapentin. The pregabalin absorption after oral intake is not saturable and the bioavailability is virtually complete. These pharmacokinetic characteristics make the suggested dose (300 mg/day) and the dose increments meaningful and the results far more predictable [21]. Therefore, in daily clinical practice, pregabalin is a better option than gabapentin.

Among the antidepressants, international guidelines provide the same level of recommendation for non-selective tricyclic antidepressants and serotonin-noradrenalin reuptake inhibitors (SNRIs). Most clinical trials showed that the efficacy of SNRIs is lower than that of tricyclic antidepressants, with a combined number needed to treat (NNT) value of about 6.4 for the SNRIs and 3.6 for tricyclic antidepressants [4]. However tricyclic antidepressants in elderly patients often provoke dizziness, sedation, orthostatic hypotension, dry mouth, and, most of all, constipation, to a level that may cause withdrawal (nortriptyline, with less-anticholinergic effects and sedation, is better tolerated than nonselective tricyclic antidepressants) [22]. Furthermore, tricyclic antidepressants are contraindicated in patients with glaucoma, prostate hypertrophy, or some cardiac conduction disturbances. Conversely, the safety profile of SNRI is far higher than that

of tricyclic antidepressants. A meta-analysis including three studies on duloxetine (i.e., the most widely used SNRI for neuropathic pain) in patients with painful diabetic neuropathy showed that at the daily dosage of 60 mg the number needed to harm (NNH) is 17.5 [23]. Furthermore, the most recent studies did not show differences in efficacy among the different antidepressants. For these reasons, due to the better safety profile and the possible lack of differences in the efficacy, SNRIs might be preferable to tricyclic antidepressants in elderly patients [24, 25].

### BEYOND NNT AND NNH: QOL IMPROVEMENT IS A REAL NEED, NOT A BONUS

Commonly used measures of therapeutic efficacy and safety of an intervention include the NNT and the NNH. However, the use of NNT in relation to neuropathic pain has been criticized [24]. To calculate the NNT, a binary outcome is required. However, in the case of pain relief, the response is gradual. This can be resolved by introducing a cut-off, and pain relief of  $\geq 50\%$  has been used in most clinical trials, as recommended by relevant regulatory bodies. Despite this, the variability and low precision of measurement techniques used in various clinical trials substantially decreases the validity of comparisons of clinical efficacy based on NNT values [24]. In addition, the heterogeneity of various neuropathic pain conditions means that a summary NNT value for neuropathic pain used in some meta-analyses has little practical meaning [24].

The outcome measure that has received relatively little attention in relation to neuropathic pain is health-related quality of life (QoL). Even though there is consistent evidence that neuropathic pain is associated with decreased QoL, there is some disagreement on whether the impact on QoL correlates with the severity of pain [3]. The process of uncovering the pathophysiological mechanisms underlying the association of neuropathic pain with anxiety and depression has only just begun, and most of the work has been carried out in animal

models [25]. It is likely that poor analgesic efficacy of pharmacological treatments is one of the major factors contributing to poor QoL in this population [3]. Since decreased QoL in patients with neuropathic pain leads to societal costs [3], development of interventions able to effectively address the impaired QoL in patients with neuropathic pains must become a priority.

### COMBINATION THERAPY: AN UNDER-RESEARCHED SOLUTION

There is some evidence that at least 45% of patients with neuropathic pain are treated with two or more drugs [26]. According to a Delphi panel of six Danish pain specialists, combination therapies are commonly used in the treatment of neuropathic pain, often with good results [27]. A systematic review that evaluated the efficacy, tolerability, and safety of combination therapies in the treatment of neuropathic pain based on the results of 21 randomized controlled clinical trials found that existing evidence supports the use of two-drug combinations in this indication [28]. Due to the small number of clinical studies that focused on any one specific combination, the authors refrained from recommending any particular treatment approaches [28]. In contrast, a meta-analysis conducted by NeuPSIG identified only seven eligible randomized controlled trials [4]. Combination therapy received an inconclusive GRADE recommendation due to conflicting findings in these studies [4].

Combination therapy can provide several advantages relative to single-drug treatments [29]. These include greater analgesic activity (due to complimentary or mutually reinforcing effects of the drugs) and a more favorable tolerability profile, as well as improvement in other symptoms such as anxiety, depression, and sleep disturbance [29]. Given the widespread use of polypharmacy in patients treated for neuropathic pain, as well as the relatively low efficacy of single-drug therapies, greater research focus on the effectiveness and safety of combination therapies is required.

## CONCLUSIONS

Neuropathic pain is a widespread condition that has a negative impact on those affected. Although a number of professional organizations have produced clinical practice guidelines for diagnosis and treatment of neuropathic pain, several methodological and conceptual issues limit their applicability in routine clinical practice, as well as the reliability of the evidence on which these guidelines are based. Development of novel pharmacological interventions is necessary to address the current issues surrounding the treatment of neuropathic pain, including low efficacy of pain relief and the poor QoL in those affected.

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