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Guidelines for the Pharmacological Treatment of Peripheral Neuropathic Pain: Expert Panel Recommendations for the Middle East Region

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

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Guidelines for the Pharmacological Treatment of Peripheral Neuropathic Pain: Expert Panel Recommendations for the Middle East Region

Neuropathic pain (NeP) has been the focus of extensive basic and clinical research over the past 20 years. This has led to an increased understanding of underlying pathophysiological mechanisms and the development of new therapeutic agents, as well as a clearer definition of the role of established medications. To date there are no published treatment guidelines for NeP in the Middle East. A multidisciplinary panel of Middle East and international experts met to review critically and reach a consensus on how best to apply evidencebased guidelines for the treatment of NeP (mainly peripheral NeP) in the Middle East. The expert panel recommended pregabalin, gabapentin and secondary amine tricyclic antidepressants (nortriptyline and desipramine) as first-line treatments for peripheral NeP. Serotonin–norepinephrine reuptake inhibitor antidepressants, tramadol and controlled-release opioid analgesics were recommended as secondline treatments. There is a need to increase diagnostic awareness of NeP, use validated screening questionnaires and undertake more treatment research in the Middle East region.

Types and causes of peripheral and central neuropathic pain syndromes

Peripheral nervous system	Central nervous system
Focal and multifocal lesions	Spinal cord injury
Diabetic mononeuropathy	Stroke (brain infarction, spinal infarction)
Post-herpetic neuralgia	Multiple sclerosis
Cranial neuralgias (such as trigeminal neuralgia, glossopharyngeal neuralgia)	Parkinson's disease
Chronic low-back pain with neuropathic component	Surgical lesions (such as rhizotomy, cordotomy)
Nerve entrapment syndromes (e.g. cervical radiculopathy, carpal tunnel syndrome)	
Plexopathy from malignancy or radiation	**Complex neuropathic disorders**
Phantom limb pain post-amputation	Complex regional pain syndrome types I and II
Post-traumatic neuralgia (such as nerve root compression, post-thoracotomy)	
Ischaemic neuropathy	
Generalized polyneuropathies	
Metabolic/nutritional	
Diabetes mellitus	
Amyloid	
Nutritional deficiencies (e.g. pellagra, beriberi)	
Hypothyroidism	
Chemical/toxic	
Alcohol	
Heavy metal poisoning	
Chemotherapy (e.g. cancer or tuberculosis treatment)	
Antiretroviral drugs	
Infectious/autoimmune	
Human immunodeficiency virus (HIV)	
Acute inflammatory polyneuropathy	
(Guillain-Barré syndrome, neuroborreliosis)	
Hereditary (Fabry's disease)	
Malignancy (carcinomatosis)	
Other (idiopathic small fibre neuropathy)	

*NEP: Neuropathic Pain, MER : Middle East Region

Pharmacological Treatment of Peripheral Nep :

Recommendations of Western Treatment Guidelines

In the past few years, four evidence-based treatment guidelines for NeP have been published in the Western literature by Danish pain experts, by the European Federation of Neurological Societies (EFNS), by the IASP and by the Canadian Pain Society. All guidelines formulated their first-line treatment recommendations based on an evaluation of both efficacy and tolerability.

physician to improve their sleep hygiene. Insomnia has been shown to contribute significantly to pain severity and should be considered an important therapeutic target in its own right. Improvement in insomnia is an important additional therapeutic benefit of treatment with pregabalin and gabapentin. The EFNS guidelines emphasize the importance of evaluating the broader effect of pharmacological treatment on overall functional and quality of life measures in patients with NeP. Based on these criteria, $\alpha_2\delta$-ligand drugs have more data supporting improvement in quality of life in NeP patients than TCAs, duloxetine or opioid analgesics.

Evidence-based treatment guidelines for peripheral neuropathic pain : comparative recommendations from Western literature

Guideline	Finnerup *et al.*, 2005	EFNS Attal *et al.*, 2006	IASP Dworkin *et al.*, 2007	CPS Moulin *et al.*, 2007
First-line treatment	**DPN and PHN :** pregabalin, gabapentin, TCA **PHN only :** topical lidocaine (for local allodynia)	**DPN and PHN :** pregabalin, gabapentin, TCA **PHN only :** topical lidocaine (for local allodynia)	**DPN and PHN :** pregabalin gabapentin, TCA **DPN only :** duloxetine, venlafaxine **PHN only :** topical lidocaine (for local allodynia)	Pregabalin, gabapentin, TCA
Second-line treatment	Tramadol, oxycodone, IRNS	**DPN and PHN :** tramadol, sdioipo **DPN only :** SNRI, lamotrigine **PHN only :** capsaicin, valproate	**DPN and PHN :** tramadol, sdioipo	SNRI, topical lidocaine

EFNS, European Federation of Neurological Societies; IASP, International Association of the Study of Pain; CPS, Canadian Pain Society; DPN, diabetic peripheral neuropathy; PHN, post-herpetic neuralgia; TCA, tricyclic antidepressants; SNRI, serotonin–norepinephrine reuptake inhibitor.
Cenral neuropathic pain (e.g. central post-stroke pain and spinal cord injury): the most evidence of efficacy is for pregabalin and gabapentin; also some evidence of efficacy for serotonin-norepinephrine reuptake inhibitor antidepressants and tricyclic antidepressants.

Peripheral NEP in the MER : First- and Second-line Treatment Recommendations

First-line treatment: $\alpha_2\delta$-ligands (pregabalin or gabapentin)

For patients diagnosed with peripheral NeP, the recommended first-line treatment is with one of the two available $\alpha_2\delta$-ligands, pregabalin or gabapentin. In contrast to gabapentin, pregabalin has linear pharmacokinetics, and also may be taken using a twice-daily dosing schedule. Furthermore, pregabalin is 2.5-times more potent than gabapentin based on plasma concentration (Wesche D, Brockbrader H, 2005, personal communication). Pregabalin is, therefore, preferred because of ease of use, patient compliance, and its more favourable pharmacokinetic and pharmacological profile.

It is important to note that both pregabalin and gabapentin must be cautiously used in NeP patients with renal insufficiency. In these patients, the initial dose must be reduced and the titration must be slower to a lower maximal dose. The initial dose may also need to be reduced in the elderly.

For all patients, regardless of the drug used for treatment, it is important that the physician provides adequate time to achieve a response, typically 2-8 weeks, with at least 1-2 weeks at the maximum tolerated dosage. In some patients with severe pain, as-needed transient dosing with opioid analgesics may be useful during the first 1-2 weeks of titration. This is best presented as an additional tool that the physician is giving the patient to help them regain a sense of control over their own lives, rather than letting the pain control them. As part of this multidisciplinary approach, patients should also be encouraged to increase their physical activity as much as possible and to work with the

Finally, the cost-effectiveness of pregabalin has been compared with generic gabapentin in two separate studies of patients with NeP due to painful DPN or PHN. In both studies, one in Spain and one in Canada, treatment with pregabalin was found to be more cost-effective than gabapentin, because the health and economic benefits of the greater number of pain-free days among patients treated with pregabalin significantly outweighed its additional cost.

First-line treatment: TCAs (nortriptyline or desipramine)

The TCAs may also be chosen as a first-line treatment for peripheral NeP and appear to have an analgesic effect that is both independent of their antidepressant effect and occurs at a lower dose range. TCAs may be preferred as a first-line treatment for patients with severe renal insufficiency since they are primarily hepatically metabolized and not renally excreted.

When choosing a TCA, secondary amines, such as nortriptyline or desipramine, are preferred because they are better tolerated than tertiary amine TCAs (amitriptyline and imipramine). This is especially true in elderly patients who are sensitive to the higher central (cognitive and memory impairing) and peripheral (constipating) anticholinergic effects of tertiary amine TCAs. The elderly are also at increased risk of injury due to falls caused by orthostatic blood pressure changes commonly occurring with both secondary and tertiary amine TCAs.

When considering a patient for treatment with a TCA, it is important to take into account the potential for drug-drug interactions, especially when co-administered with drugs that inhibit CYP2D6 enzyme.

The safety issue of greatest concern is the risk of cardiac toxicity (arrhythmias, myocardial infarction) associated with TCA treatment, even at therapeutic doses. In light of this risk, it is recommended that the lowest effective dose of a TCA should be used.

Treatment with TCAs is contraindicated in patients with ischaemic heart disease, arrhythmias, those at increased risk of sudden cardiac death or in anyone who has suicidal ideation or a past history of suicide attempts. A screening ECG is recommended before beginning treatment with TCAs in patients > 40 years of age. For patients with painful DPN only, treatment with duloxetine may offer an alternative with a more favourable benefit–risk profile than the TCAs.

First-line treatment : topical lidocaine for focal PHN with allodynia

In patients who present with focal PHN with allodynia, or any peripheral NeP associated with a small, localized area of allodynia, treatment with topical lidocaine (patch or a 5% gel or cream) may be chosen as a firstline treatment. Topical lidocaine is minimally absorbed, so adverse events are uncommon, as long as the skin is not blistered or excessively inflamed.

Second-line treatment : SNRI antidepressants (venlafaxine XR or duloxetine)

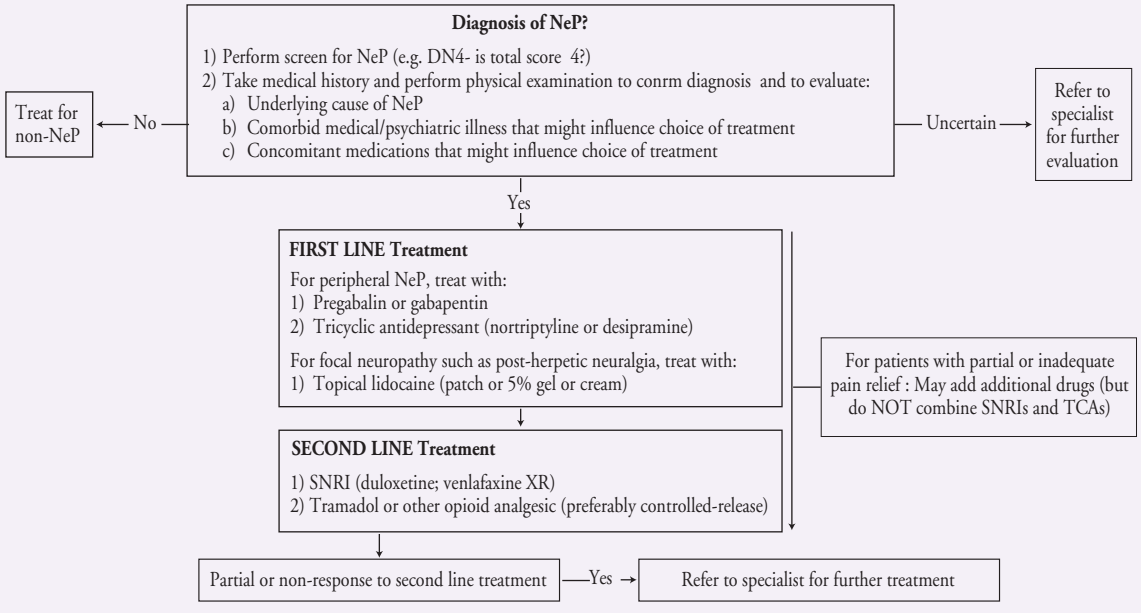
The SNRI antidepressants may be considered as second-line treatments. They share the same dual serotonin and norepinephrine reuptake inhibiting mechanism as the TCAs, but have a superior safety profile with notably less anticholinergic effects, and less cardiovascular risk). More evidence for efficacy in peripheral NeP is available for duloxetine than for venlafaxine XR, although studies of the former drug are limited to painful DPN. Future studies of duloxetine showing efficacy in other neuropathic pain syndromes may elevate it to first-line treatment status. Drug-drug interactions are relatively common with duloxetine, since it inhibits CYP2D6 metabolism, and thus raises the plasma levels of drugs that use this common metabolic pathway. Duloxetine is also contraindicated in liver disease and severe renal disease, and treatment may be associated with elevated liver enzymes and worsening glycaemic control in diabetes patients. The most common adverse events occurring during treatment with duloxetine are nausea, somnolence, dizziness, fatigue and headache, insomnia and sexual dysfunction. Both duloxetine and venlafaxine XR carry strong warnings about a paradoxical increased suicide risk, but this serious safety concern is reported to be much more common in young patients (< 25 years).

Second-line treatment : opioid analgesics (tramadol, oxycodone or others)

Opioid analgesics are generally considered second-line treatments because of the high risk of physical tolerance, addiction and the potential for abuse. In general, controlled-release formulations are preferred. Patients often escalate their opioid analgesic dose over time and dose reduction must be undertaken with great care to avoid a withdrawal reaction and a rebound in pain intensity. Dose escalation is also associated with an increase in cognitive and psychomotor impairment. Oxycodone is a potent μ-agonist that has demonstrated efficacy in peripheral NeP. Tramadol is a less potent μ-agonist, but shares some of the monoamine reuptake inhibiting properties of the TCAs. Because of its lower μ-agonist activity, tramadol may have lower risk of abuse than oxycodone. Recent research has found that peri-operative treatment with pregabalin and gabapentin effectively reduces post-operative pain and reduces use of opioid analgesics. The impact of treatment with $\alpha_2\delta$-ligand drugs on the level of use of opioid analgesics in NeP patients has not been well studied.

Peripheral NeP in the MER : Developing a treatment algorithm

First- and second-line treatment recommendations may be summarized in a simplified treatment algorithm. The first step, as noted in the algorithm, is to establish that the patient presenting with pain has an NeP diagnosis. This requires that the physician corrects for any potential tendency to underestimate the severity and impact of the patient's pain complaint.



Simplified treatment algorithm for peripheral neuropathic pain : Stepwise management (NeP, neuropathic pain; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant)

Furthermore, it requires that the physician takes the time systematically to evaluate the presence of NeP symptoms and the distribution and underlying causes of the pain. As previously noted, this evaluation should include completion of the DN4 screening test or the pain DETECT questionnaire screener if the primary complaint is chronic low-back pain. The patient-rated questionnaire screener, ID Pain, may also be used.

Once a diagnosis of peripheral NeP has been made, a first-line treatment, such as pregabalin or gabapentin, should be chosen as summarized above. Patients should typically be treated for 2-8 weeks, with at least 1-2 weeks at the maximum tolerated dosage, then evaluated to determine the degree of pain relief that has been achieved. As a general rule, patients who achieve minimal-to-no pain relief on the first-line treatment are candidates for switching to a second-line drug such as a controlled-release formulation of an opioid analgesic or an SNRI antidepressant. Alternatively, if some pain relief has been achieved and the first-line drug is welltolerated, then a second-line drug may be added to the first-line drug. The combination therapies with the most empirical support are gabapentin and morphine and gabapentin and nortriptyline. It is important to note, however, that combined therapy tends to be associated with higher risks in terms of safety and tolerability. Furthermore, there is insufficient research available to guide physicians in making an evidence-based decision as to what is the optimal next-step treatment: (i) between-class or within-class switching to a new drug; or (ii) augmentation therapy by the addition of a second drug.

If at all feasible, a general practitioner should refer any patient who continues to have an inadequate response to a specialist for further therapy, since further treatment strategies are likely to become increasingly complex. If referral is not feasible, then the general practitioner may consider a trial and error approach in which various combinations of first- and second-line therapies are tried. They may also consider the use of various third-line treatments as summarized in previous treatment guidelines. These third-line treatments have much weaker evidence for efficacy and often have significant safety issues. Third-line treatments include various anti-epilepticdrugs such as carbamazepine, lamotrigine, oxcarbazepine, topiramate and valproate; antidepressant drugs such as bupropion, citalopram and paroxetine and miscellaneous other medications such as mexiletine, N-methyl-D-aspartate receptor antagonists and topical capsaicin.

In addition to third-line treatments, there are multiple other medications that have been used clinically over the years for the treatment of NeP. Among the most common are non-steroidal anti-inflammatory drugs such as diclofenac, naproxen, ibuprofen and aspirin, as well as vitamin B. There is minimal-to-no evidence that any of these medications have any benefit and they are not recommended for use in the treatment of NeP.

Central NeP : treatment recommendations

The treatment of central NeP is not the primary focus of this article because there have been insufficient placebo-controlled RCTs conducted to make strong evidencebased recommendations. Based on the limited available research, the first-line treatment would appear to be pregabalin or gabapentin. Other treatments, such as opioid analgesics, and SNRIs or TCAs may also have efficacy in central NeP, but the benefit appears to be notably less than for peripheral NeP.

Discussion

The current article has summarized the consensus agreement of an expert panel on applying evidence-based guidelines for the treatment of peripheral NeP in the MER. In light of the general practice resources available in the MER, the expert panel arrived at its consensus recommendations by evaluating each treatment option across the following four dimensions: (i) efficacy, based on the results of placebo-controlled RCTs; (ii) safety, based on tolerability, low potential for drug-drug interactions and low risk of serious medical side-effects; (iii) effectiveness in treating commonly occurring comorbid conditions, such as depression, anxiety and insomnia as well as the ability to enhance overall quality of life; and (iv) ease of use and convenience.

Taking these four dimensions into consideration, pregabalin was the consensus recommendation by this expert panel for first-line treatment of peripheral NeP. Gabapentin was also a first-line recommendation, but pregabalin was preferred due to its more favourable pharmacokinetics and ease of use. Furthermore, two separate studies have found pregabalin to be a more cost-effective treatment than gabapentin.

Treatment with topical lidocaine was recommended as a first-line treatment for patients presenting with focal PHN with allodynia. Nortriptyline and desipramine (secondary amine TCAs) were also recommended as first-line treatments, especially in the presence of depression. The choice of a TCA is only recommended, however, after a careful benefit–risk evaluation has been made, especially in elderly patients.

The SNRI antidepressants and opioid analgesics, including tramadol, were the consensus second-line treatment recommendation. Patients should typically be treated for 2-8 weeks, with at least 1-2 weeks at the maximum tolerated dosage. In patients who have shown at least some clinically meaningful response to the firstline treatment, adding a second-line drug was a possible treatment choice, but only after a careful benefit–risk assessment has been made. The importance of nonpharmacological approaches was emphasized as being crucial to the success of pharmacological pain management. Nonpharmacological approaches include training in stress reduction techniques, sleep hygiene and physical therapy. Furthermore, physicians are encouraged to work collaboratively with their NeP patients, providing them with realistic information on what to expect from treatment in terms of both efficacy and adverse events. A collaborative approach gives patients a sense of control that is crucial to the success of any pain management programme.

Source: *The Journal of International Medical Research 2010; 38: 295-317*

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EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

Neuropathic pain (NP) may be caused by a lesion or a disease of the somatosensory system and is estimated to afflict as high as 7–8% of the general population in Europe. The management of NP is challenging because the response to most drugs remains unpredictable despite attempts to develop a more rationale therapeutic approach. In 2006, the European Federation of Neurological Societies (EFNS) produced the first guidelines on pharmacological treatment of NP. Since 2006, new randomized controlled trials (RCTs) have appeared in various NP conditions, justifying an update.

Classification of evidence for drug treatments in commonly studied neuropathic pain (NP) conditions and recommendations for use.
Treatments are presented in alphabetical order. Only drugs used at repeated dosages are shown here (with the exception of treatments with longlasting effects such as capsaicin patches). Drugs marked with an asterisk were found effective in single class II or III studies and are generally not recommended. Drugs marked with two asterisks are not yet available for use.

Aetiology	Level A rating for efficacy	Level B rating for efficacy	Level C rating for efficacy	Level A/B rating for in efficacy or discrepant results	Recommendations for first line	Recommendations for second or third line
Diabetic NP[a]	Duloxetine, Gabapentin-morphine, TCA, Gabapentin, Nicotine agonist**, Nitrate derivatives**, Oxycodone, Pregabalin, TCAb, Tramadol alone or with acetaminophen, Venlafaxine ER	Botulinum toxin* Dextromethorphan Gabapentin/venlafaxine* Levodopa*	Carbamazepine Phenytoin	Capsaicin cream, Lacosamide, Lamotrigine, Memantine, Mexiletine, Mianserin, NK1 antagonist**, Oxcarbazepine, SSRI, Topical clonidine, Topiramate, Valproate, Zonisamide	Duloxetine Gabapentin Pregabalin TCA Venlafaxine ER	Opioids Tramadol[c]
PHN	Capsaicin 8% patch**, Gabapentin Gabapentin ER**, Lidocaine plasters Opioids (morphine, oxycodone, methadone), Pregabalin, TCAb	Capsaicin cream Valproate*	Benzydamide topical Dextromethorphan Fluphenazine Memantine Lorazepam Mexiletine COX-2 inhibitor** Tramadol	Gabapentin Pregabalin TCA Lidocaine plasters[d]	Capsaicin Opioids	Opioids Tramadol[c]
Classical trigeminal neuralgia	Carbamazepine	Oxcarbazepine	Baclofen* Lamotrigine* Pimozide* Tizanidine*	----------	Carbamazepine Oxcarbazepine	Surgery
Central pain	Cannabinoids (oro-mucosal **, oral) (MS) Pregabalin (SCI)	Lamotrigine (CPSP) TCA (SCI, CPSP) Tramadol (SCI)* Opioids	----------	Carbamazepine, Gabapentin Lamotrigine (SCI), Levetiracetam Mexiletine, S-ketamine iont. Valproate	Gabapentin Pregabalin TCA	Cannabinoids (MS) Lamotrigine Opioids Tramadol (SCI

The objectives of our revised Task Force were (i) to examine all the RCTs performed in various NP conditions since 2005, (ii) to propose recommendations aiming at helping clinicians in their treatment choice for most NP conditions, and (iii) to propose studies that may clarify unresolved issues.

Painful polyneuropathy

Painful polyneuropathy (PPN) is a common NP condition. Diabetic and non-diabetic PPN are similar in symptomatology and with respect to treatment response, with the exception of HIV-induced neuropathy.

HIV neuropathy

Most initial trials of HIV neuropathy were negative (Table 1). Only lamotrigine was moderately effective in patients receiving antiretroviral treatment. Recent RCTs found efficacy of smoked cannabis (1–8% tetrahydrocannabinol for 5 days) on pain intensity but not mood or functioning. A one-off application of high concentration (8%) capsaicin patch applied to the feet for 30, 60 or 90 min was superior to low concentration (0.04%) in the 30- and 90-minute group from weeks 2 to 12 without detectable changes in sensory thresholds. However, another study reported in a systematic review was negative on the primary outcome.

Recommendation. We recommend TCA, gabapentin, pregabalin and SNRI (duloxetine, venlafaxine) as first line treatment in PPN (notably related to diabetes) (level A).

Tramadol (level A) is recommended second line except for patients with exacerbations of pain (for the tramadol/acetaminophen combination) or those with predominant coexisting non-neuropathic pain (in view of its largely established efficacy in nociceptive pain). Third-line therapy includes strong opioids because of concerns regarding their long-term safety including addiction potential and misuse, which warrants further RCTs. Treatments with drug with no or equivocal effect are listed in Table. In HIV-associated polyneuropathy, only lamotrigine (in patients receiving antiretroviral treatment) (level B), smoking cannabis (level A) and capsaicin patches (level A) were found moderately useful.

Post-herpetic neuralgia

Post-herpetic neuralgia is a common aftermath of herpes zoster in the elderly.

*EFNS = European Fedaration of Neurological Societies

Recommendation

We recommend TCA or gabapentin/pregabalin as firstline treatment in PHN (level A). Topical lidocaine (level A, less consistent results) with its excellent tolerability may be considered first line in the elderly, especially if there are concerns regarding the CNS side effects of oral medications. In such cases, a trial of 2–4 weeks before starting other therapy is justified. Strong opioids (level A) and capsaicin cream are recommended as second choice. Capsaicin patches are promising (level A), but the long-term effects of repeated applications particularly on sensation are not clarified.

Trigeminal neuralgia

Trigeminal neuralgia (TN) typically presents with very brief attacks of pain (electric shocks) and is divided into classic when secondary to vascular compression of the trigeminal nerve in the cerebellopontine angle or when no cause is found, or symptomatic when secondary in particular to cerebellopontine angle masses or multiple sclerosis.

Recommendation

In agreement with previous guidelines, carbamazepine (level A) and oxcarbazepine (level B) are confirmed first line for classical TN. Oxcarbazepine may be preferred because of decreased potential for drug interactions. Patients with intolerable side effects may be prescribed lamotrigine (level C) but should also be considered for a surgical intervention. We deplore the persistent lack of RCTs in symptomatic TN.

Central neuropathic pain

The most frequent central neuropathic pain (CP) states are caused by stroke (central post-stroke pain, CPSP), spinal cord injury (SCI) or multiple sclerosis (MS).

Recommendation

We recommend pregabalin (level A), amitriptyline (level B, level A in other NP conditions) or gabapentin (level A in other NP conditions) as first line in CP. Tramadol (level B) may be considered second line. Strong opioids (level B) are recommended second or third line if chronic treatment is not an issue. Lamotrigine may be considered in CPSP or SCI pain with incomplete cord lesion and brush-induced allodynia (level B) and cannabinoids in MS (level A) only if all other treatments fail.

Cancer NP : There is level A evidence for the efficacy of gabapentin (one study), level B for TCA and tramadol and inefficacy of valproate. Traumatic NP : Gabapentin was reported to be ineffective on the primary outcome in a large multicentre trial but improved several secondary outcomes and may be beneficial in a subgroup of patients (level A) although predictors of the response need to be identified; antidepressants have level B evidence, good results were reported for botulinum toxin A and discrepant or negative results were obtained with other drugs. Radiculopathy: Pregabalin (level A), TCA and opioids and their combination (level B) are ineffective or slightly effective (the combination TCA/opioids was effective on maximal pain only in one study). Phantom pain: Efficacy of tramadol and morphine was reported (level A), while gabapentin induced discrepant results. Results in multi-aetiology NP are positive mainly for antidepressants (bupropion, TCA), opioids (levorphanol, methadone) and cannabinoids.

Effects on pain symptoms and signs and predictors of the response

Randomized controlled trials increasingly assess symptoms and signs and suggest that drugs (gabapentin, oxycodone, topical lidocaine, cannabinoids) have differential effects on the quality of NP (i.e., burning, deep, paroxysmal)and that some may alleviate brush-induced and/or static mechanical allodynia based on single trials (TCA, pregabalin, cannabinoids, topical lidocaine, venlafaxine, NMDA antagonists but not lamotrigine). Although predictors of response to some drugs (e.g., opioids, lidocaine plasters) were identified in post hoc analyses, no RCT has yet been designed to detect predictive factors of the response based on baseline phenotypic profile (level C).

Final recommendations and issues for future trials

The present revised EFNS guidelines confirm TCA (25–150 mg/day), gabapentin (1200–3600 mg/day) and pregabalin (150–600 mg/day) as first line for various NP conditions (except for trigeminal neuralgia, section 3) and lidocaine plasters (up to 3 plasters/day) first line in PHN particularly in the elderly. We now are able to recommend SNRI (duloxetine 60–120 mg/day, venlafaxine 150–225 mg/day) first line in painful diabetic polyneuropathies based on their more established efficacy. TCA raise safety issues at high doses and in the elderly, they are not more effective than gabapentin based on one comparative trial, but they are less costly.

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CONGRATULATIONS!!!

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