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

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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 evidence-based 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 second-line 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.

KEY WORDS: Antidepressants; Anticonvulsants; Pregabalin; Gabapentin; Nortriptyline; Desipramine; Neuropathic pain; Middle East; Consensus; Guidelines

Introduction

The International Association for the Study of Pain (IASP) defines neuropathic pain (NeP) as 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'.[1] The direct effect of NeP on the somatosensory system is in contrast to what occurs in patients with inflammatory or nociceptive pain, in which the primary damage is to non-neuronal tissue. NeP may be peripheral or central in origin, and may be caused by a wide range

of diseases (e.g. diabetes mellitus, herpes zoster, human immunodeficiency virus [HIV], post-stroke), trauma or other injury (e.g. cervical radiculopathy, chronic low-back pain, carpal tunnel syndrome, spinal cord injury), or medical or surgical interventions (e.g. chemotherapy, phantom limb post-amputation) (Table 1).[1,2]

Confidence in the diagnosis of NeP depends on the history and examination of the patient presenting with a complaint of pain. A clinical grading system of 'possible', 'probable' or 'definite' NeP has recently been suggested.[1] A grade of 'possible NeP' is when the patient reports a history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system and the neuroanatomic distribution of pain

TABLE 1:
Types and causes of peripheral and central neuropathic pain syndromes[2,14,25]

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	
Phantom limb pain post-amputation	
Post-traumatic neuralgia (such as nerve root compression, post-thoracotomy)	
Ischaemic neuropathy	
Generalized polyneuropathies	**Complex neuropathic disorders**
Metabolic/nutritional	Complex regional pain syndrome types I and II
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)	

symptoms is consistent with the history. A grade of 'probable NeP' is if one of the following additional criteria are met: (i) sensory signs on neurological examination confirm the self-reported symptoms; or (ii) a laboratory or other diagnostic test confirms an underlying lesion or disease that explains the NeP. A grade of 'definite NeP' is when both criteria (i) and (ii) are met.[1]

The past decade has seen a marked increase in the number of placebo-controlled, randomized clinical trials (RCTs) designed to evaluate the efficacy and safety of various pharmacological treatments for NeP. Meta-analyses of available RCTs have been reported for multiple drugs[3 – 10] and evidence-based recommendations have been further summarized in treatment guidelines.[2,11 – 13] Nonetheless, as O'Connor and Dworkin[14] have recently pointed out, significant gaps in the literature still remain, including: (i) the relative lack of RCTs that provide a head-to-head comparison of drugs from different classes; (ii) the relative lack of RCTs evaluating the efficacy for NeP conditions other than diabetic peripheral neuropathy (DPN) or post-herpetic neuropathy (PHN); (iii) the relative lack of long-term RCTs that evaluate how well initial improvement is sustained; and (iv) the relative lack of RCTs that systematically evaluate optimal next-step treatment for non-responders.

In the treatment guideline literature, the most notable gap appears to be the exclusive focus on recommendations for managing NeP patients in Europe and North America. One of the few exceptions we are aware of is a practice guideline recently published by a group of Latin American experts.[15] No similar NeP guideline is available for the Middle East region (MER).

Guidelines are a crucial mechanism for translating the results of RCTs into standardized and optimized clinical practice. The clinical presentation of a disorder such as NeP occurs in quite variable circumstances, and exists in a complex social, cultural and economic ecosystem. Thus, guidelines must be region-specific to ensure that they are tailored to the needs of a given region. This is especially important for the treatment of pain conditions since significant ethnic and cross-cultural differences have been identified in the perception of pain.[16] Furthermore, the types of diseases and injuries that cause NeP exhibit a high-degree of cross-national variance. For example, rates of diabetes in the MER are among the highest of any region in the world.[17,18]

The objectives of this article are: (i) briefly to review what is known about the prevalence and clinical presentation of NeP in the MER; (ii) to summarize the recommendations of an expert panel for applying evidence-based guidelines for the treatment of peripheral NeP in the MER; and (iii) to highlight key clinical areas for future research. For the purposes of the current guidelines, the MER was defined as including the following countries: Bahrain, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Oman, Qatar, Saudi Arabia, Sudan, Syria, United Arab Emirates and Yemen, with an aggregate population > 300 000 000.

Materials and methods

EXPERT PANEL

An expert panel was convened in Dubai, United Arab Emirates, on 8 October 2009. The panel comprised a multidisciplinary group with clinical and research expertise in the diagnosis and treatment of NeP, and included eight physicians from the MER, as well as two international experts (one from France and one from Canada). The panel included physicians interested in pain

management from different specialties, including neurologists, endocrinologists, internists, family physicians, pain specialists and community medicine specialists.

LITERATURE SEARCH

The expert panel reviewed available RCTs and evidence-based guidelines on the treatment of peripheral NeP. Additional publications were identified via searches of Medline and the Cochrane Database. The Medline (PubMed) database was searched using the terms: pain (acute, chronic, neuropathic); clinical trials OR meta-analysis OR practice guideline; drug classes and individual drug names, specifically, antidepressant drugs, antiepileptic drugs, anticonvulsant drugs, opiates, analgesic drugs, N-methyl-D-aspartate (NMDA) receptor antagonists; and gabapentin, pregabalin, nortriptyline, amitritpyline, desipramine, lidocaine, duloxetine, venlafaxine, oxycodone, tramadol, carbamazepine, lamotrigine, topiramate, valproate/valproic acid, phenytoin, mexiletine, capsaicin.

DATA COLLATION

Dr Edward Schweizer (Paladin Consulting Group, Hoboken, New Jersey, USA) was responsible for collating all of the experts' comments into a preliminary draft document which was circulated to the authors for review. The authors provided edits and feedback on content they agreed or disagreed with and, on the basis of these edits, the document was revised until the language of the document met the consensus approval of all authors.

Results

NeP: EPIDEMIOLOGY IN THE MER

Comparative prevalence rates for selected NeP syndromes are summarized in Fig. 1.[19–23] While extensive epidemiological data are available from Western studies, relatively little data are available on the prevalence of NeP in the MER: two studies of diabetic patient samples (93% of diabetes patients had type 2) reported widely different rates of painful DPN of 36%[20] and 65%;[21] two additional studies reported a high incidence

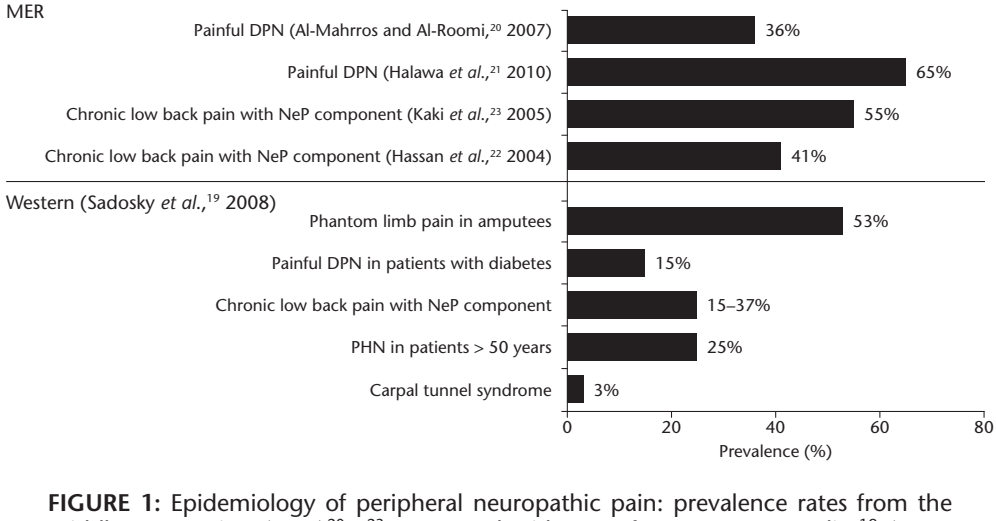


FIGURE 1: Epidemiology of peripheral neuropathic pain: prevalence rates from the Middle East region (MER)[20–23] compared with rates from Western studies[19] (DPN, diabetic peripheral neuropathy; PHN, post-herpetic neuralgia; NeP, neuropathic pain)

(41 – 55%) of a neuropathic pain component in patients with chronic low-back pain.[22,23] MER rates for NeP in both diabetes and chronic low-back pain were notably higher than rates typically reported in Western patient populations.[19] These few available studies, which suggest regional differences in NeP prevalence, illustrate the importance of conducting region-specific epidemiological assessments.

Similar regional differences have also been reported in a study of the cross-national burden of painful DPN.[24] In that study, individuals from the MER had notably higher pain severity ratings, and pain-related impairment in quality of life and functioning, than patients in Asia or the UK.[24]

NeP: PATHOPHYSIOLOGY

As noted above, NeP is caused by direct damage to, or pathological changes in, the somatosensory nervous system. This somatosensory damage triggers not just pain, but a range of associated signs and symptoms. Both peripheral and central sensitization of pain pathways may contribute to NeP.[25] Peripherally, pain sensations are carried by unmyelinated (C-fibres) or thinly myelinated (Aδ) fibres. In NeP, these neurons become sensitized by disease or injury, and develop abnormal excitability and increased sensitivity to mechanical or thermal stimuli. Peripheral nerve injury may also cause a release of inflammatory cytokines and glutamate from glial cells. Central sensitization occurs when acute or chronic pain stimuli cause an exaggerated response in the central pain pathways that ascends from the dorsal horn neurons via the spinothalamic tract (STT) up to the thalamus. The pathophysiology of NeP involves long-lasting changes in the membrane excitability of dorsal horn neurons that process incoming pain stimuli. Large Aβ nerve fibres, that typically carry non-pain stimuli (e.g. pressure, light touch), are also recruited to carry pain-related stimuli. Further contributing to the development of NeP is a loss of inhibitory modulation of incoming pain sensations, which may result in spontaneous discharges of hyperexcited STT neurons.[25]

NeP: DIAGNOSIS

Pain is one of the most frequently occurring symptom complaints in the general practice setting, occurring in approximately 35 – 40% of all patient visits.[26,27] In a large cross-national study, represented by only one country from the MER, chronic pain > 6 months in duration was reported by 22% of non-elderly general practice patients, and at a higher rate (29%) in the MER.[28]

Studies suggest a physician bias in estimating both the severity and chronicity of patient pain. In one general practice study,[29] the Spearman correlation coefficient between physician and patient pain ratings was 0.20 for chronic pain. On a 100-mm visual analogue scale, 37% of physicians graded pain intensity as > 20 mm lower than their patients rated their pain and 20% graded pain as > 40 mm lower than their patients did.[29]

To make an accurate diagnosis of NeP in patients who present with a chief complaint of pain, physicians must take a careful history that systematically defines the distribution of the pain, characterizes its qualitative features, and identifies the underlying causal illness or injury and any associated comorbidities.[2,25] Table 2 summarizes the signs and symptoms that typically occur in patients diagnosed with NeP.[30] The presence of oedema and autonomic symptoms, such as sweating, flushing and warmth suggest the presence of

TABLE 2:
Typical symptoms and signs in patients diagnosed with neuropathic pain

	Typical symptoms and signs	
Medical term	**English**	**Arabic**
Allodynia (pain from a non-painful stimulus)	Cold is painful, light touch or something brushing on skin is painful	احساس بالالم في مكان ليس مؤلما عادة
Analgesia (absence of pain response to a painful stimulus)	Numbness to painful stimulus	عدم الاحساس بالالم
Anaesthesia (total loss of sensation, especially tactile)	Numbness to touch, pinprick, temperature and/or vibration	لا يوجود احساس مطلقا
Dysaesthesias and/or spontaneous pain (unpleasant and/or painful sensation)	Burning or shooting pain, electric shocks, itching (may occur spontaneously with no evident stimulus)	الم بدون مسبب / الم تلقائي
Hypoalgesias (reduced sensitivity to a painful stimulus)	Reduced sensitivity/numbness to pain (Aδ-fibres; C-fibres)	نقص الاحساس بالالم
Hyperalgesias (increased sensitivity to a painful stimulus)	Lower pain threshold or increased intensity of response above the usual threshold	زيادة في مستوى الاحساس بالالم
Hypoaesthesias (reduced sensitivity to a non-painful stimulus)	Reduced sensitivity to touch or vibration (Aβ-fibres), pinprick or cold (Aδ-fibres), or warmth (C-fibres)	نقص في الاحساس
Paraesthesias (abnormal sensation that is not unpleasant or painful)	Tingling, 'ants crawling', pins and needles (may occur spontaneously with no evident stimulus)	احساس بالتنميل

Adapted from Merskey and Bogduk.[30]

complex regional pain syndrome, type I or II. Trophic changes are also commonly observed.[2,25]

Two screening tools are useful for physicians in general practice for identifying patients with a possible diagnosis of NeP: the DN4 screening test;[31] and the pain*DETECT* questionnaire.[32,33] The DN4 screening test is a brief 10-item questionnaire that can be completed in < 5 min (Fig. 2). Patients with a score of ≥ 4 have a 90% chance of having a diagnosis of NeP. It is, however, important to note that 17% of patients who actually have a diagnosis of NeP only achieve a score of 2 or 3 and, thus, will not be identified using the DN4 screen (these patients are the 'false negatives' on the test). It should also be noted that the probability that the patient has a diagnosis of NeP is > 90% if the DN4 score is 5 (93%) or 6 (98.5%).[31] The overall accuracy of the DN4 as a screening test for NeP compares favourably with other

Interview questions for the patient:
Question 1: Does your pain have one or more of the following characteristics?

	Yes (1)	No (0)
1. Burning		
2. Cold is painful		
3. Electric shocks		

Question 2: Is the pain associated with one or more of the following symptoms in the same area?

	Yes (1)	No (0)
4. Tingling		
5. Pins and needles		
6. Numbness		
7. Itching		

Examination of the patient:
Question 3: Is the pain located in an area where the physical examination had one or both of the following characteristics?

	Yes (1)	No (0)
8. Hypoaesthesia to touch		
9. Hypoaesthesia to pinprick		

Hypoaesthesia: decreased sensitivity

Question 4: In the painful area, can the pain be caused or increased by:

	Yes (1)	No (0)
10. Brushing		
Total score =		

Total score ≥ 4: 90% probability of neuropathic pain.

FIGURE 2: The DN4 screening test for neuropathic pain.[31] This questionnaire is reproduced with permission of the International Association for the Study of Pain® (IASP®) and may not be further reproduced for any purpose without permission of the IASP®

screening tests that are widely used in general practice, such as the Papanicolaou test to detect malignant or pre-malignant cervical lesions, or electrocardiography (ECG) as a screening test for myocardial infarction.[34,35] The DN4 screening test has been translated into Arabic and validated in Middle East populations.[21] Given the prevalence of NeP in the MER among high risk groups, such as diabetes patients, screening for NeP is highly recommended by the current expert panel.

The pain*DETECT* questionnaire (Fig. 3) has similar accuracy to the DN4 screening test, but its validated use is limited to patients presenting with chronic low-back pain. A total score of 19 is associated with a 90% probability that the back pain has a NeP component; however 16% of patients with a NeP component will achieve a score ≤ 18 (i.e. 'false negatives' on the test).[32]

A useful patient-rated NeP screening questionnaire, the ID Pain, has also been validated (Fig. 4).[36] The ID Pain questionnaire contains six items that require a 'yes' or 'no' answer. Patients whose total score is in the range 3 – 5 have a 69% probability of having a diagnosis of NeP. As expected, the predictive validity of the scale is lower than physician screening instruments, such as the DN4, but

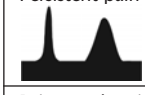
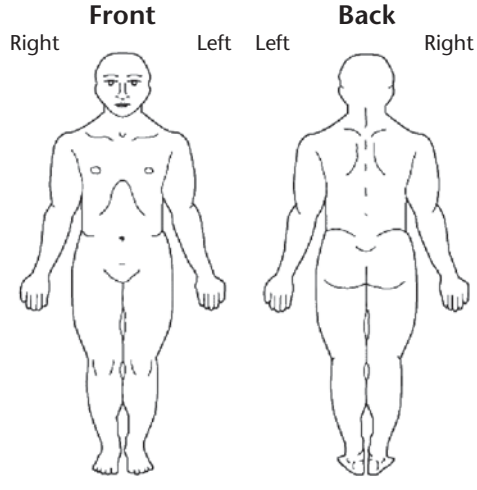
Rate the severity of your pain:	Never 0	Hardly noticeable 1	Slightly 2	Moderately 3	Strongly 4	Very strongly 5
Do you suffer from a burning sensation (e.g. stinging nettles) in the marked areas?						
Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?						
Is light touching (clothing, a blanket) in this area painful?						
Do you have sudden pain attacks in the area of your pain, like electric shocks?						
Is cold or heat (bath water) in this area occasionally painful?						
Do you suffer from a sensation of numbness in the areas that you marked?						
Does slight pressure in this area, e.g. with a finger, trigger pain?						
Please select the picture that best describes the time course of your pain:	**Circle 'yes'**					
Persistent pain with slight fluctuations: 	Yes = 0 points					
Persistent pain with pain attacks: 	Yes = –1 point					
Pain attacks without pain between them: 	Yes = +1 point					
Pain attacks with pain between them: 	Yes = +1 point					
	No 0	**Yes 2**				
Does your pain radiate to other regions of your body?						
TOTAL SCORE =						

FIGURE 3: The pain*DETECT* questionnaire: a screening test for neuropathic pain.[32] Validated use limited to patients presenting with chronic low-back pain (total score > 19 associated with 90% probability of neuropathic pain)

the results are acceptable for a patient-rated screener and may be useful in busy general practice settings.

In addition to taking a careful patient history, a brief but systematic neurological examination is essential for making a diagnosis of NeP. The goal of the examination is three-fold: (i) to identify the specific pain-related sensory changes summarized in Table 2 (e.g. hypoaesthesias,

On the diagram, below, shade in the areas where you feel pain. If you have more than one area, circle the area that bothers you the most.



Mark 'Yes' to the following items that describe your pain over the past week and 'No' to the ones that do not.

Question	Score	
	Yes	No
1. Did the pain feel like pins and needles?	1	0
2. Did the pain feel hot/burning?	1	0
3. Did the pain feel numb?	1	0
4. Did the pain feel like electrical shocks?	1	0
5. Is the pain made worse with the touch of clothing or bed sheets?	1	0
6. Is the pain limited to your joints?	–1	0

Total score = 3–5: 69% probability of NeP (using c-index)

FIGURE 4: ID Pain – a patient-rated questionnaire for neuropathic pain (NeP).[36] If the patient scores a total score of 3 – 5, then there is a 69% probability of NeP (using c-index)

hypoalgesias, hyperalgesias); (ii) to delineate the somatic distribution of these sensory changes and the related pain; and (iii) to identify signs that might assist in diagnosing the underlying cause of the NeP (if the cause has not already been diagnosed). The tools used for this evaluation are simple and consist of a finger or monofilament (for light stroking), a pin to test the effect of a pain stimulus, and warm and cold objects to test for changes in thermal thresholds and responsivity.[2,25] Additional tests, such as electromyography, nerve conduction studies and quantitative sensory testing, may be useful for confirming the nerve lesion, but they are not necessary or sufficient alone for making the diagnosis of NeP.[2,13]

PHARMACOLOGICAL TREATMENT OF PERIPHERAL NEP: RECOMMENDATIONS OF WESTERN TREATMENT GUIDELINES

In the past few years, four evidence-based treatment guidelines for NeP have been

TABLE 3:
Evidence-based treatment guidelines for peripheral neuropathic pain: comparative recommendations from Western literature[11 – 13,37]

Guideline	Finnerup *et al.*,[37] 2005	EFNS Attal *et al.*,[11] 2006	IASP Dworkin *et al.*,[12] 2007	CPS Moulin *et al.*,[13] 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, SNRI	**DPN and PHN:** tramadol, opioids **DPN only:** SNRI, lamotrigine **PHN only:** capsaicin, valproate	**DPN and PHN:** tramadol, opioids	SNRI, topical lidocaine
Criteria used in formulating guideline	1. Efficacy, based on NNT analysis of RCTs 2. Tolerability, based on NNH analysis of RCTs	1. Number of positive high quality RCTs (NNT calculated) 2. Side-effect profile (calculated as the ratio of efficacy-to-safety) 3. Effect on comorbidities and QoL	1. Number of positive high quality RCTs (grade A evidence) 2. Safety, tolerability 3. Drug–drug interactions 4. Ease of use 5. Impact on health-related QoL 6. Clinical experience of the authors	1. Number of positive high quality RCTs 2. Side-effect profile 3. Ease of use 4. Cost

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; NNT, number needed to treat; RCTs, randomized clinical trials; NNH, number needed to harm; QoL, quality of life.
Central 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.[2]

published in the Western literature (Table 3): by Danish pain experts,[37] by the European Federation of Neurological Societies (EFNS),[11] by the IASP,[12] and by the Canadian Pain Society.[13] All guidelines were based on a review of published double-blind, placebo-controlled RCTs; each of the guidelines reviewed a similar total sample of > 100 RCTs. All guidelines formulated their first-line treatment recommendations based on an evaluation of both efficacy and tolerability. Two of the guidelines[11,37] relied on a 'number needed to treat' (NNT) analysis as the benchmark, however, the EFNS guideline[11] adjusted for low (more favourable) NNT values for classes of drugs such as the tricyclic antidepressants (TCAs) that were attributable to multiple studies with small sample sizes. All four guidelines noted that safety and tolerability were taken into consideration, with one guideline[37] formally calculating 'number needed to harm' values, while other guidelines took other variables into consideration such as ease of use,[12,13] drug–drug interactions and the 'clinical experience' of the experts,[12] and effect on comorbidities and quality of life.[11,12]

PERIPHERAL NeP: GENERAL TREATMENT CONSIDERATIONS

Several key treatment considerations are highlighted in guidelines endorsed by the American Pain Society, the Canadian Pain Society, the Finnish Pain Society, the Latin American Federation of IASP Chapters and the Mexican Pain Society.[12] First, is the crucial importance of careful patient evaluation and accurate diagnosis for the successful treatment of NeP; use of validated scales, such as the DN4 screening test, are highly useful tools to assist in achieving an appropriate diagnosis. Secondly, it is important to identify and treat underlying disease processes that may be contributing to the clinical presentation of NeP. Thirdly, it is important to identify comorbid conditions that frequently complicate the clinical course of NeP and may respond differentially to specific NeP treatments; three of the most common comorbid conditions are depression, anxiety and sleep disturbance. Fourthly, drug therapy of NeP is much more likely to be successful if the patient is educated about the underlying causes of NeP, and is given realistic information on what to expect from treatment in terms of both efficacy and adverse events. Furthermore, patients should be educated about non-pharmacological approaches, including stress reduction, sleep hygiene and physical therapy.[2]

PERIPHERAL NeP: SPECIFIC TREATMENT RECOMMENDATIONS

The choice of a specific medication as a first- or second-line treatment takes into account several factors such as: (i) the potential for medication-related adverse events, including physical dependence and/or abuse; (ii) the potential risk of drug–drug interactions; (iii) the presence of comorbid conditions (e.g. depression, anxiety, sleep disturbance) that may also be relieved by the medication; and (iv) the potential medical risk associated with use of high doses and/or overdose. The cost of individual drugs is a country-specific consideration.[38] It should be noted, however, that it is frequently difficult accurately to model the net cost-offset value of pharmacological interventions, especially since use of a more effective (albeit more costly) drug may prevent an even more costly visit to an emergency department, or an inpatient hospitalization, or may prevent the development of a disability that results in loss of employment.[39]

Table 3 summarizes the first- and second-line treatment recommendations from four published Western guidelines.[11 – 13,37] Two

classes of drugs are consistently recommended as first-line treatments for peripheral NeP (DPN and PHN) across all four guidelines: pregabalin and gabapentin ($\alpha_2\delta$-ligands) and the TCAs. For patients with localized PHN, topical lidocaine is also recommended as a first-line treatment by all four guidelines. One guideline recommends the serotonin–norepinephrine reuptake inhibitor (SNRI) antidepressants (duloxetine, venlafaxine), which share the same dual serotonin/norepinephrine reuptake inhibition mechanism as the TCAs, as a first-line treatment only for DPN.[12] The other three guidelines recommend SNRIs as second-line treatment, along with opioid analgesics and tramadol (Table 3).[11,13,37]

PERIPHERAL NEP IN THE MER: FIRST- AND SECOND-LINE TREATMENT RECOMMENDATIONS

Optimally adapting Western NeP treatment guidelines to the Middle East requires that region-specific variables are taken into account and these fall into three broad categories: (i) potential differences in the clinical presentation, typical comorbidity rates and course of NeP illness; (ii) potential differences in the pharmacological effects of the drugs; and (iii) differences in the medical culture of the region. Differences in pharmacological effects may be attributable to genetic factors, such as polymorphisms in cytochromes P450 (CYP450) enzymes that yield very different metabolic rates for various drugs. For example, individuals from the MER have been found to have different frequencies of *CYP2D6* allele variations compared with other ethnic groups (e.g. Asians, Africans), yielding different proportions of individuals who are poor versus rapid versus ultra-rapid metabolizers.[40,41] This is not relevant for drugs such as pregabalin that are primarily renally cleared, however most of the other drugs used to treat NeP undergo hepatic metabolism. Potential differences in treatment effects may also be attributable to non-genetic factors relating to cultural differences in diet and exercise habits, rates of smoking and alcohol consumption, hepatic and renal function, and rates of obesity and metabolic syndrome. Finally, in terms of clinical presentation and comorbidity, it appears that rates of both diabetes[42] and major depressive disorder[43] are both higher in the MER compared with other regions and, as previously noted, there are marked ethnic and cultural differences in pain perception.[16]

Unfortunately, detailed and reliable information across all three broad categories of variables is not known. However, taking what is known into account and considering the totality of evidence regarding efficacy, safety and tolerability, and ease of use, yields the following 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 (Table 4). 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

TABLE 4:
First- and second-line treatments for peripheral neuropathic pain: summary of recommended therapeutic use in the Middle East region

Drug class	Dosing	Adverse effects (incidence > 10%)	Drug–drug interactions	Precautions	Other efficacy
α2δ-ligands (first-line treatment)					
Pregabalin	**Start:** 75 mg twice daily or 50 mg three times daily **Increase by:** 150 mg/day every 3 – 7 days as tolerated **Max. dose:** 300 mg twice daily or 200 mg three times daily	Dizziness, sedation, peripheral oedema	No PK interactions. Additive psychomotor effects when given with alcohol, opioids, or benzodiazepines	Suicide risk; reduced dose in renal insufficiency	Insomnia efficacy Anxiolytic efficacy
Gabapentin	**Start:** 100 – 300 mg three times daily **Increase by:** 300 – 900 mg/day every 1 – 7 days as tolerated **Max. dose:** 1200 mg three times daily	Dizziness, sedation, peripheral oedema	No PK interactions. Additive psychomotor effects when given with alcohol, opioids, or benzodiazepines	Suicide risk; reduced dose in renal insufficiency	
Tricyclic antidepressants (first-line treatment)					
Nortriptyline or desipramine	**Start:** 25 mg at bedtime **Increase by:** 25 mg/day every 3 – 7 days as tolerated **Max. dose:** 150 mg at bedtime (may need blood levels to optimize dose)	Dry mouth, constipation, blurred vision, sedation, weight gain, urinary retention, dizziness	Anti-arrhythmics; SSRI/SNRI or MAOI antidepressants; cisapride; pimozide	Suicide risk; overdose risk arrhythmia; contraindicated in glaucoma; relative contraindication in elderly due to cardiovascular risk and risk of cognitive impairment due to anticholinergic effect	Antidepressant efficacy

TABLE 4 (continued):
First- and second-line treatments for peripheral neuropathic pain: summary of recommended therapeutic use in the Middle East region

Drug class	Dosing	Adverse effects (incidence > 10%)	Drug–drug interactions	Precautions	Other efficacy
Topical lidocaine (first-line treatment)					
Lidocaine patch (5%)	Apply 1 – 3 patches for up to 12 h/day	Local rash, redness	None (due to minimal systemic absorption)	Do not apply patch over inflamed or blistered skin; use cautiously in severe hepatic disease	None
SNRI antidepressants (second-line treatment)					
Duloxetine (also venlafaxine XR, though less evidence is available)	**Start:** 60 mg/day **Increase by:** None **Max. dose:** 60 mg/day	Dry mouth, nausea, constipation, fatigue, sedation, dizziness, headache	Tramadol; TCAs; SSRIs; SNRIs; duloxetine inhibits metabolism of drugs metabolized by CYP2D6	Suicide risk Some risk of hypertension, increased bleeding, and reduction in glucose control (in diabetes patients) In patients with substantial alcohol use or chronic liver disease	Antidepressant efficacy

TABLE 4 (continued):
First- and second-line treatments for peripheral neuropathic pain: summary of recommended therapeutic use in the Middle East region

Drug class	Dosing	Adverse effects (incidence > 10%)	Drug–drug interactions	Precautions	Other efficacy
Opioid analgesics (second-line treatment)					
Oxycodone	**Start:** 5 – 15 mg every 4 – 6 h **Increase by:** 5 – 15 mg/day every 3 – 7 days as tolerated **Max. dose:** No fixed max. dose since tolerance develops to analgesic effects	Constipation, nausea, vomiting, sedation, dizziness, pruritus	Alcohol, other CNS or respiratory depressants	High risk of addiction and abuse; high risk of withdrawal reaction with rebound worsening of pain if discontinued after long-term use (> 2 – 3 months). Recommend tapering by 25% per day. Risk of overdose with respiratory and CNS depression; psychomotor impairment	None
Tramadol	**Start:** 25 mg in the morning **Increase by:** 25 mg/day every 3 days as tolerated **Max. dose:** 100 mg four times daily	Dizziness/vertigo, nausea, vomiting, constipation, sedation	Alcohol, other CNS or respiratory depressants; TCAs or SSRI/SNRI antidepressants	Precautions similar to other opioid analgesics, but with lower severity and frequency of risk	

PK, pharmacokinetics; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin–norepinephrine reuptake inhibitor; MAOI, monoamine oxidase inhibitor; TCA, tricyclic antidepressant; CYP, cytochrome P450; CNS, central nervous system.

insufficiency (Table 4). 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.[44]

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.[2] 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,[2] patients should also be encouraged to increase their physical activity as much as possible and to work with the physician to improve their sleep hygiene.[45] Insomnia has been shown to contribute significantly to pain severity[46] 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.[44,47] 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.[11,48]

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.[49,50] 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 (Table 4), and appear to have an analgesic effect that is both independent of their antidepressant effect and occurs at a lower dose range.[13] 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.[51]

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).[12,14] 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.[52,53] 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,[54] and the multiple safety precautions summarized in Table 4. The safety issue of greatest concern is the risk of cardiac toxicity (arrhythmias, myocardial infarction) associated with TCA treatment, even at therapeutic doses.[12,55] 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.[55] For patients with painful DPN only, treatment with duloxetine may offer an alternative with a more favourable benefit–risk profile than the TCAs.[12]

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 first-line treatment (Table 4). Topical lidocaine is minimally absorbed, so adverse events are uncommon, as long as the skin is not blistered or excessively inflamed.[56]

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

The SNRI antidepressants may be considered as second-line treatments (Table 3). 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 (Table 4). 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.[57] Future studies of duloxetine showing efficacy in other neuropathic pain syndromes may elevate it to first-line treatment status.[2] 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.[57] 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.[57] 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).[58]

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 (Table 4). 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.[14] Tramadol is a less potent μ-agonist, but shares some of the monoamine reuptake inhibiting properties of the TCAs.[6,9] Because of its lower μ-agonist activity, tramadol may have lower risk of abuse than oxycodone.[14] Recent research has found that peri-operative treatment with pregabalin and gabapentin effectively reduces post-operative pain and reduces use of opioid analgesics.[59] 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 (Fig. 5). 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. Furthermore, it requires that the physician takes the time systematically to evaluate the presence of NeP symptoms (Table 2), and the distribution and underlying causes of the pain. As previously noted, this evaluation should include completion of the DN4 screening test (Fig. 2),[21,31] or the pain*DETECT* questionnaire screener (Fig. 3)[32,33] if the primary complaint is chronic low-back pain. The patient-rated questionnaire screener, ID Pain, may also be used (Fig. 4).[36]

Once a diagnosis of peripheral NeP has been made, a first-line treatment, such as pregabalin or gabapentin, should be chosen as summarized above and in Fig. 5. Patients should typically be treated for 2 – 8 weeks, with at least 1 – 2 weeks at the maximum tolerated dosage,[2] 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

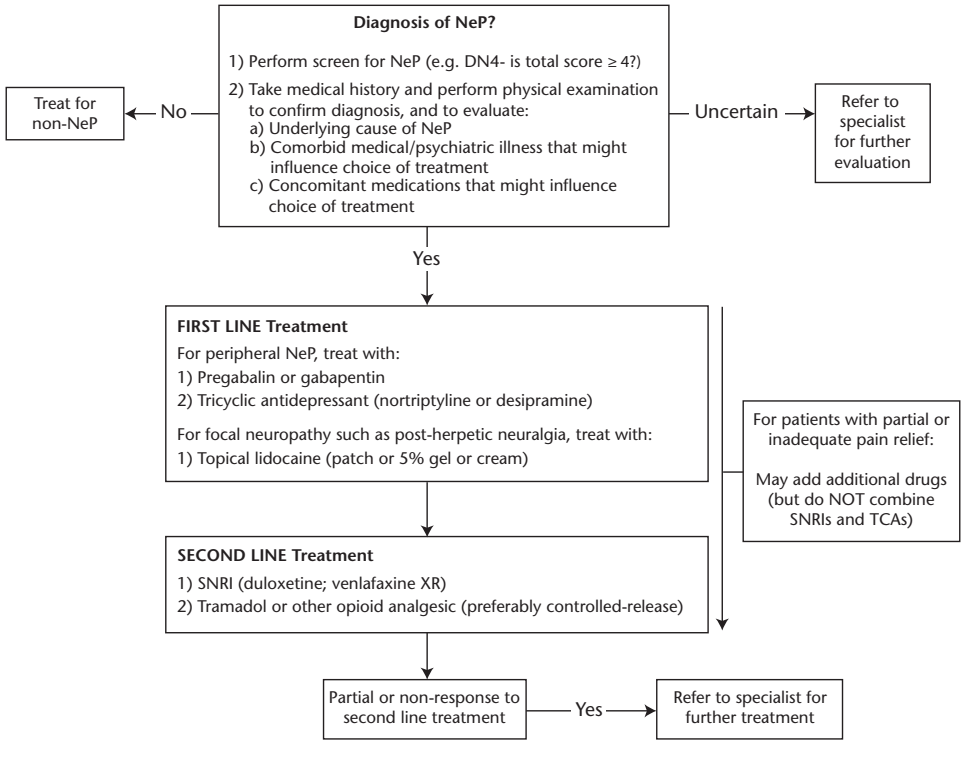


FIGURE 5: Simplified treatment algorithm for peripheral neuropathic pain: stepwise management (NeP, neuropathic pain; SNRI, serotonin–norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant)

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 well-tolerated, then a second-line drug may be added to the first-line drug.[2,12,13] The combination therapies with the most empirical support are gabapentin and morphine,[60] and gabapentin and nortriptyline.[61] 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.[11 – 13,37] These third-line treatments have much weaker evidence for efficacy and often have significant safety issues. Third-line treatments include various anti-epileptic drugs 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.[2,11]

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 evidence-based recommendations.[62] Based on the limited available research, the first-line treatment would appear to be pregabalin or gabapentin.[10,62 – 66] 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.[2,67]

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.[68] Furthermore, two separate studies have found pregabalin to be a more cost-effective treatment than gabapentin.[49,50]

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.[52 – 55]

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 first-line 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 non-pharmacological approaches was emphasized as being crucial to the success of pharmacological pain management. Non-pharmacological 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.

Finally, the expert panel noted an urgent need for more research on the prevalence of various types of NeP in the MER. The absence of data on the prevalence of NeP in the MER and its burden of illness may contribute to lack of awareness among primary care physicians. Medical help-seeking is typically high among patients experiencing pain, but it is uncertain whether there is adequate recognition and formal diagnosis of NeP by primary care physicians in the MER. While patients may report a chief complaint of pain, physicians need the screening tools and the diagnostic approach that will encourage them systematically to characterize the distribution of the pain, to characterize its qualitative features (burning, tingling, painful response to light touch or cold), and to perform the key elements of a neurological examination. Under-diagnosis inevitably leads to inadequate treatment resulting, all too often, in frequent switching of medications and/or premature reliance on the use of opiates. The lack of research in the MER is not only limited to the epidemiology, clinical presentation and burden of illness of NeP, but there are also limited adequately powered, placebo-controlled RCTs of MER populations with NeP. The current treatment guidelines should be considered a preliminary recommendation until such region-specific data are available.

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Conflicts of interest

Dr Bohlega reports receiving honoraria as a speaker from Pfizer and Novartis. Dr Moulin reports receiving grant/research funding from Pfizer and Purdue, speaker honoraria from Boehringer-Ingelheim, Merck Frosst and Valeant, and consulting fees from Pfizer, Purdue and Janssen-Ortho. Dr Alsaadi reports receiving consultation fees and honorarium from GlaxoSmithKline, Pfizer, Novartis, Cyberonics and Janssen Cilag. Dr Shelbaya reports receiving grant/research funding and consulting and speaker fees from Sanofi-Aventis and MSD. Drs Hosny, Riachi, Amir, Salti and Karawagh have no conflicts of interest to declare in relation to this article.

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