The dos and don’ts of painful diabetic peripheral neuropathy: Primary care guidelines for the Middle East and North Africa

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Abstract

Background: Diabetes mellitus (DM) is becoming increasingly common in developing countries and is of major concern in the Middle East and North Africa (MENA). Since at least 30% of diabetic patients may develop painful diabetic peripheral neuropathy (pDPN) within their lifetime, there is an urgent need to increase awareness of the condition among physicians in the region.

Objectives: To increase awareness of physicians in the Middle East and North Africa of the increasing prevalence of DM and pDPN and to provide practical consensus recommendations to facilitate the diagnosis and management of pDPN.

Methods: A panel of family medicine physicians was convened in Dubai to discuss current awareness of pDPN in the region and to develop consensus statements based on a review of meta-analyses, systematic reviews, and evidence-based guidelines on the screening, diagnosis and management of pDPN.

Recommendations: The panel recommends that all patients with diabetes be screened at least annually for symptoms of neuropathic pain using screening tools such as the Doleur Neuropathique en 4 Questions (DN4) as well as thorough examination of the patient’s feet. Treatment should aim to achieve a clinically meaningful reduction in pain using first-line agents including pregabalin, duloxetine or tricyclic antidepressants.

Conclusion: pDPN is common but under-diagnosed and inadequately treated in the Middle East and North Africa. Physicians in the region are encouraged to implement screening for pDPN and manage patients according to published guidelines.

Key words: Painful diabetic neuropathy, Middle East, North Africa, neuropathic pain, consensus recommendations
Introduction

Once considered a ‘disease of affluence’, diabetes mellitus (DM) is becoming increasingly common in developing countries and is of major concern in the Middle East and North Africa. (1) Complications of diabetes include cardiovascular disease, nephropathy and retinopathy, but the most commonly encountered complication is diabetic peripheral neuropathy (DPN). (2) and it is estimated that approximately 30% of diabetic patients have painful diabetic peripheral neuropathy (pDPN). (2-6) Clinically, DPN is a diagnosis of exclusion, defined as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes”. (7) pDPN has a significant negative impact on quality of life by reducing patients’ mobility and ability to perform everyday tasks, increasing the risk of foot ulcers and amputation, disturbing sleep and causing psychological distress. (3, 8)

pDPN is widely under-diagnosed and often poorly treated. A survey conducted by the American Diabetes Association in 2005 found that up to 75% of patients who experienced pDPN symptoms were not diagnosed and that 56% of these patients were not even aware of the condition. (5) Other studies have also shown that patients who do receive treatment are often dissatisfied with the outcomes. (6, 9) The few studies of pDPN that have been conducted in Middle Eastern and North African countries suggest prevalence ranges from 22-65%, reflecting different populations and methods of diagnosing this condition, but may also indicate true differences from the expected prevalence of approximately 30%. (1, 10-12)

The present review and clinical guidelines aim to increase awareness of pDPN among physicians in the Middle East and North Africa as well as to provide practical consensus recommendations to facilitate the diagnosis and management of pDPN in the region.

Materials and Methods

A panel of seven family medicine physicians from the Middle East and North Africa, together with Professor Rayaz A. Malik from Weill Cornell Medicine in Doha, Qatar and NY, USA, was convened in Dubai, United Arab Emirates, on 17 October 2015. The panel members had extensive clinical and research expertise in the diagnosis and management of pDPN in the general practice setting, while Professor Malik, who is a member of the writing group for the 2016 American Diabetes Association consensus statement on diabetic neuropathy, was an advisor to the panel. The key objectives of the meeting were to gain a better understanding of the most pressing challenges facing family medicine practitioners in the region regarding the management of pDPN in their day-to-day clinical practice and to develop consensus recommendations to optimize diagnosis and treatment.

The panel discussed 6 pertinent themes:

1) the current state of awareness of pDPN among physicians in the region,
2) key features of patient presentations with pDPN,
3) issues and challenges facing physicians with respect to screening for neuropathic pain,
4) goals and routine management strategies,
5) problems with initiating and maintaining treatment, and
6) methods for optimizing the patient-physician relationship based on evidence-based guidelines on the screening, diagnosis and management of pDPN.

Figure 1: Estimated prevalence of pDPN among patients with diabetes mellitus in countries in the Middle East and North Africa (1, 10, 13)
Epidemiology
Estimates of the prevalence of pDPN vary widely in the region due to a paucity of data. Moreover, current prevalence rates may be underestimated as patients often do not approach their physicians with symptoms of neuropathic pain and many remain undiagnosed. The worldwide prevalence of pDPN among patients with DM is estimated to be around 30%, however in the Middle East and North Africa this ranges from 22.5-65% (Figure 1). (1, 10, 13)

Of note, most data have been gathered from patients in secondary and tertiary care centers and studies in primary care are required to establish the true prevalence of pDPN.

Etiology and risk factors
The exact etiology of pDPN is unknown and may be attributable to a combination of chronic hyperglycemia and cardiovascular risk factors such as dyslipidaemia and hypertension. (18)

The Diabetes Control and Complications Trial (DCCT) and its follow-up study, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, showed that intensive glycemic control can delay the development and progression of diabetic neuropathy in patients with type 1 DM (T1DM). (19, 20) However, patients with type 2 DM (T2DM) do not seem to benefit from intensive glycemic control as per a Cochrane meta-analysis and several large clinical trials. (4, 21, 22) Lipid levels, blood pressure, inflammation, insulin resistance, oxidative stress, vitamin D deficiency, height, cigarette smoking, and alcohol consumption have all been related to pDPN in various studies. (2, 10, 22-24)

Epidemiological analyses suggest that the following are significant risk factors for pDPN(25):
- long-standing diabetes of ≥10 years’ duration
- age ≥65 years
- body mass index (BMI) ≥30
- female sex

Pathophysiology
The exact mechanisms underlying pDPN remain unclear, but both the peripheral and central nervous system are thought to be involved. Painful sensations can arise from damage to the A and C nerve fibers. Lesions of the peripheral nerves can increase their excitability, a phenomenon known as peripheral sensitization. This occurs via increased or altered sodium channel expression and function, which is associated with spontaneous painful discharges and reduced thresholds for activation leading to neuropathic pain. (26) Increased calcium channel expression also encourages the release of excitatory neurotransmitters such as glutamate and substance P, and can increase the excitability of neurons in the spinal cord (central sensitization). (23, 27)

Efferent nerve fibers that descend from the brain to the dorsal horn of the spinal cord have a powerful inhibitory effect on pain signals sent via the afferent fibres; their function is reliant on neurotransmitters such as γ-aminobutyric acid (GABA), serotonin, and noradrenaline. Dysfunction of these pathways can also result in central sensitization. (27)

Clinical presentation
Patients with pDPN tend to describe their symptoms using similar terms and most describe either numbness or a tingling, electric shock-like, burning, shooting or stabbing pain in their feet or lower legs due to the involvement of the small sensory nerve fibers (Table 1). (5, 28, 29)
A classic ‘stocking - glove’ distribution of pain is expected with symptoms initially occurring in the toes, feet and lower limbs and in advanced cases progressing to the fingers and hands.(4) Many patients report that their symptoms are worse at night.(5, 28, 29)

**Practice points: Typical symptoms of pDPN**
Symptoms vary among patients but typically include at least one of the following:
- Numbness
- Tingling sensation
- Shooting/Stabbing pain
- Burning sensation

**Other characteristics**
- Worse at night
- Stocking - glove distribution: Starts in the feet, progresses up the lower limbs.
Table 2: Conditions to be ruled out when considering a pDPN diagnosis

<table>
<thead>
<tr>
<th>Diagnosis and evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A comprehensive physical examination should be performed when a patient with diabetes presents with neuropathic pain. A careful clinical history should be undertaken as the differential diagnoses are many and varied, and diagnosis may be challenging (Table 2).</td>
</tr>
</tbody>
</table>

The first step in assessing a patient is to determine whether there is any evidence of neuropathic pain. Neuropathic pain can be distinguished from nociceptive pain by using a screening tool and performing a thorough clinical examination (Table 3).

Table 3: Tests to be performed before diagnosing pDPN

<table>
<thead>
<tr>
<th>Basic tests</th>
<th>Advanced confirmatory tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood cell count</td>
<td>Electromyography</td>
</tr>
<tr>
<td>Comprehensive metabolic panel</td>
<td>Corneal confocal microscopy</td>
</tr>
<tr>
<td>Vitamin B12 measurement</td>
<td>Skin biopsy</td>
</tr>
<tr>
<td>Serum protein electrophoresis with immunofixation</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose measurement</td>
<td></td>
</tr>
<tr>
<td>Glucose tolerance test</td>
<td></td>
</tr>
</tbody>
</table>
It is recommended that all patients with metabolic syndrome/impaired glucose tolerance and Type 1/2 diabetes should be screened for neuropathic pain at least annually. A number of different screening tools are available that can aid with differentiating neuropathic and nociceptive pain including the Neuropathic Pain Questionnaire, the Leeds Assessment of Neuropathic Pain and Symptoms scale and the McGill Pain Questionnaire. (18, 25)

The Doleur Neuropathique en 4 Questions (DN4) scale is recommended as it has a sensitivity and specificity of 82.9% and 89.9%, respectively, and validated translations are available in 15 languages, including English, Arabic and French (see: Appendix). (25, 29, 30) It is a 10-item questionnaire - 7 items are based on symptoms and 3 on a simple and easy to perform clinical examination. A score ≥ 4 is suggestive of neuropathic pain (Figure 4). (25)

Figure 4: English translation of the Doleur Neuropathique en 4 Questions (DN4) scale recommended for distinguishing nociceptive and neuropathic pain (29)
Clinical Assessments

Patients with pDPN present initially with pain in the feet and physicians are thus advised to remove a patient’s shoes and socks to undertake a thorough clinical examination of the patient’s feet. Tests include not only the three tests performed as part of the DN4 (testing for touch, pinprick, and allodynia), but also a more careful analysis of the patient’s description of their pain. Traditionally, a monofilament has been used for assessing neuropathy; however, this is only useful for evaluating advanced neuropathy and for identifying patients at high risk of foot ulceration. It should therefore not be used to identify neuropathy as it will often be normal despite significant small fiber neuropathy.

The 3L (listen, look, locate) approach is recommended for identifying signs and symptoms of neuropathic pain(27):

- **Listen** to the patient’s verbal description of their pain and note any mention of non-painful symptoms that are experienced in the same area as the pain.
- **Look** for any sensory abnormalities such as pain felt upon touching the sensitive area and note any unusually warm or cold regions and differences in color or texture relative to a non-painful adjacent site.
- **Locate** the region of pain and document its position using a pain drawing, which can be created by the patient or the physician. Make a note of any abnormal sensations on the drawing.

Increasing patient awareness is important for encouraging patients to self-report painful symptoms. Patients may not volunteer this information and it is recommended that physicians ensure that all at-risk patients are aware of the possibility of developing pDPN and of the symptoms they should look out for. It is also important to note that approximately 10-15% of patients with diabetes who experience neuropathic symptoms will have a neuropathy from another cause that may be treatable.

Contemporary Management

There is currently no cure for pDPN and treatment is challenging as many patients do not experience sufficient pain relief.(28, 31) In this context, combination pain relief regimens may be more effective than the traditional approach of trialing and discontinuing a single agent if this fails to provide sufficient relief.(31)

Treatment goals are focused on preventing the development or progression of DPN through an improvement in glycaemic control and vascular risk factors and educating patients as to how best to address their symptoms, employing pharmacologic and/or non-pharmacologic agents to help manage neuropathic pain to improve the patient’s QoL.(5)

**Practice points:**

**Recommendations for Clinical Assessment**

- Apply the DN4 screening tool to identify neuropathic vs nociceptive pain
- Remove the patient’s shoes and socks and examine his/her feet
- Employ the 3L approach: Listen to the vocal description of pain, locate the region of pain, and look for somatosensory deficits with the help of simple bedside tests

**Practice points:**

- **Practice points:**
  - **Red flags** indicating that referral to a neurologist is required
    - Asymmetrical pain
    - Predominance of motor vs sensory neuropathy
    - Rapid progression
    - Acute onset
    - Prominent autonomic symptoms

**Practice points:**

- Use GABA analogs (pregabalin or gabapentin), tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) first-line
- Consider combining pregabalin or gabapentin with SNRIs or TCAs
- Opioid analgesics can be given for second-line use

First- and second-line recommendations for treatment published in guidelines for the Middle East and North Africa are consistent with those used globally and are summarized in Table 4. Most recent guidelines for treating neuropathic pain - including the International Association for the Study of Pain Neuropathic Pain Special Interest Group (NeuPSIG) - recommend the use of anticonvulsant GABA analogs (pregabalin or gabapentin), serotonin-norepinephrine reuptake inhibitors (SNRIs e.g., duloxetine), or tricyclic antidepressants (TCAs) as first-line therapy. Other options include opioid analgesics (Table 5).(31, 32) Other therapies such as topical nitrate, vitamin D and alpha lipoic acid, (33, 34) as well as non-pharmacological therapy such as acupuncture, and transcutaneous electrical nerve stimulation may also have a place in treating patients with pDPN. Vitamin B is frequently used in pDPN management in the MENA region, however, there are limited data in randomized trials testing the efficacy of vitamin B for treating peripheral neuropathy and meta-analyses have reported inconclusive evidence for its role in therapy.(35)
Table 4: Global first- and second-line recommendations for the treatment of neuropathic pain associated with diabetic peripheral neuropathy (31, 32)

<table>
<thead>
<tr>
<th>Guideline</th>
<th>First-line recommendations</th>
<th>Second-line recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle East Region</td>
<td>Pregabalin, gabapentin, TCAs, lidocaine (topical)</td>
<td>SNRIs (duloxetine or venlafaxine-XR), opioid analgesics (e.g., tramadol, oxycodone)</td>
</tr>
<tr>
<td>French-speaking Maghreb</td>
<td>Pregabalin, gabapentin, TCAs, lidocaine (topical)</td>
<td>SNRIs (venlafaxine-XR or duloxetine), tramadol</td>
</tr>
<tr>
<td>European Federation of Neurological Sciences (EFNS)</td>
<td>Pregabalin, gabapentin, TCAs, SNRIs (duloxetine or venlafaxine ER), lidocaine (topical)</td>
<td>Tramadol, opioids, capsaicin patches</td>
</tr>
<tr>
<td>Canadian Pain Society (CPS)</td>
<td>Pregabalin, TCAs, gabapentin</td>
<td>SNRIs, lidocaine (topical)</td>
</tr>
<tr>
<td>American Academy of Neurology (AAN)</td>
<td>Pregabalin</td>
<td>Gabapentin, duloxetine, venlafaxine, sodium valproate, amitriptyline, tramadol, oxycodone, capsaicin</td>
</tr>
<tr>
<td>International Association for the Study of Pain (IASP)</td>
<td>Pregabalin, gabapentin, TCAs, SNRIs (duloxetine or venlafaxine)</td>
<td>Capsaicin 8% patches, Lidocaine patches, Tramadol</td>
</tr>
<tr>
<td>Special Interest Group (NeuPSIG 2015)</td>
<td>Pregabalin, gabapentin, amitriptyline, duloxetine</td>
<td>Capsaicin cream, Tramadol (acute rescue therapy)</td>
</tr>
</tbody>
</table>

**Patient counseling**

Patients should be given clear, specific information on how to use their medications as well as counseling on expectation of the response to therapy, as an expected response may be 50% at best whilst a 30% reduction in pain is considered clinically meaningful. Patients may be disappointed if they expect complete resolution of their painful symptoms.

Physicians should clarify that the agents prescribed are used for a specific purpose and that many have multiple indications: TCAs for example are prescribed for their effect on neuropathic pain not because of their antidepressant effects and this should be made clear to patients. In addition, patients should also be educated about the side effects of different medications especially when prescribed in high doses and both benefits and disadvantages should be openly discussed with the patient, to ensure compliance.

It is also important to follow-up on treatment to ensure that the prescribed medication is having the intended effect; if not, the dose should be increased or an alternative be prescribed. A simple 11-point pain scale can be useful for distinguishing ‘before’ and ‘after’ pain scores to help determine the effectiveness of the prescribed treatment.
Table 5: Summary characteristics of treatments recommended for neuropathic pain associated with diabetic peripheral neuropathy.29, 31, 32, 34, 36 EU: European Union; ME: Middle East; US: United States

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism of action</th>
<th>Dosing</th>
<th>Potential Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsant</td>
<td>Bind to calcium channels and reduce the release of several neurotransmitters</td>
<td>Pregabalin:</td>
<td>Sedation, confusion, peripheral oedema, dizziness</td>
</tr>
<tr>
<td>GABA analogs</td>
<td></td>
<td>- 150-600 mg/day in 2 or 3 divided doses (EU)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- 150-300 mg/day in 3 divided doses (US)</td>
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<tr>
<td></td>
<td></td>
<td>- 75 mg twice daily or 50 mg three times daily. Increase by 150 mg/day</td>
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<tr>
<td></td>
<td></td>
<td>every 3-7 days as tolerated. Maximum dose 300 mg twice daily or 200</td>
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<td></td>
<td></td>
<td>mg three times daily (ME)</td>
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<td></td>
<td></td>
<td>Gabapentin:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 900-3600 mg/day in 3 divided doses (EU)</td>
<td></td>
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<td></td>
<td></td>
<td>- 900-1800 mg/day in 3 divided doses (US)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- 100-300 mg three times daily. Increase by 300-900 mg/day every 1-7</td>
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<td></td>
<td></td>
<td>days as tolerated. Maximum dose 1200 mg three times daily (ME)</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>Inhibit reuptake of noradrenaline and serotonin, block sodium channels, anticholinergic</td>
<td>Amitriptyline:</td>
<td>Sedation, dry mouth, postural hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 50-200 mg/day in 2 divided doses or once at night (EU)</td>
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<td>- 75-150 mg/day in 2 divided doses or once at night (US)</td>
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<tr>
<td></td>
<td></td>
<td>- 25 mg/day at bedtime. Increase by 25 mg/day every 3-7 days as</td>
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<tr>
<td></td>
<td></td>
<td>tolerated. Maximum dose 150 mg/day at bedtime (ME).</td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td>Inhibit reuptake of noradrenaline and serotonin. Augment descending inhibitory pain pathways</td>
<td>Duloxetine:</td>
<td>Fatigue, nausea, increased sweating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 60-120 mg/day (EU)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>- 60 mg/day (US)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 60 mg/day maximum dose (ME)</td>
<td></td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>µ-opioid receptor agonist</td>
<td>Tramadol:</td>
<td>Nausea, vomiting, constipation, respiratory depression, ziness</td>
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<tr>
<td></td>
<td></td>
<td>- 100 mg in 2 divided doses</td>
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<td></td>
<td></td>
<td>- Increase every 4-7 days to a maximum of 400 mg/day (100 mg per dose 4 times per day)</td>
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<td></td>
<td>- 25 mg/day in the morning. Increase by 25 mg/day every 3 days as</td>
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<tr>
<td></td>
<td></td>
<td>tolerated. Maximum dose 100 mg four times daily. (ME)</td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Blocks sodium channels and dampens peripheral nociceptor sensitation and CNS hyperexcitability</td>
<td>5% patch</td>
<td>Skin irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Apply 1-3 patches (5%) for up to 12 h/day</td>
<td></td>
</tr>
<tr>
<td>Capsaicin</td>
<td>Deposition of the neurotransmitter substance P from primary afferent neurons and loss of epidermal innervation</td>
<td>0.075% cream applied up to 4x daily</td>
<td>Erythema, burning pain, local skin irritation</td>
</tr>
<tr>
<td>patches/cream</td>
<td></td>
<td>8% patch</td>
<td></td>
</tr>
<tr>
<td>Alpha lipoic acid</td>
<td>Selective modulation of neuronal T-type calcium channels</td>
<td>600 mg per day intravenously for 3 weeks (Grade A recommendation)</td>
<td>Nausea, vomiting, and dizziness</td>
</tr>
</tbody>
</table>
Treatment Algorithm

Patient with DM presents with chronic pain in the lower limbs

Are the patient’s verbal descriptions suggestive of neuropathic pain?

Yes

Does physical examination using simple bedside tests reveal any sensory abnormalities?

Yes

Can you actively exclude all other neuropathies?

Yes

pDPN likely: initiate treatment with a first-line agent such as an anticonvulsant, SNRI or TCA. Is this successful?

Yes

Continue treatment with regular monitoring

No

If first-line monotherapy is not successful initiate therapy with an alternative first-line therapy or combination of first-line agents

No

If combination therapy is not successful initiate therapy with second-line agents such as opioid analgesics or topical capsaicin

No

Probable nociceptive pain. Treat as appropriate (neurological exam can be normal in pDPN)

No

Probable nociceptive pain. Treat as appropriate (neurological exam can be normal in pDPN)
Discussion

pDPN is increasingly common in the Middle East and North Africa but is underdiagnosed. Physicians in the region are encouraged to familiarize themselves with the latest guidelines for diagnosing and managing the condition. The use of screening tools such as the DN4 should be combined with a comprehensive physical examination to identify patients suffering from pDPN and DPN. The 3L (listen, look, locate) approach to clinical assessment is recommended. Physicians should educate their patients on identifying pDPN to avoid unnecessary suffering with loss of sleep and a reduced QoL.

Once neuropathy has been diagnosed, causes other than pDPN should be excluded. Affected patients can be managed according to international treatment recommendations for pDPN. Anticonvulsants (such as pregabalin and gabapentin), SNRIs and TCAs are recommended for first-line treatment. Patients should be closely followed-up and those with inadequate pain relief should be offered an alternative first-line agent that has a different mechanism of action, or combination therapy. Second-line agents should be reserved for patients who suffer more severe pain and who are unable to obtain adequate relief from first-line agents either alone or in combination.

Acknowledgements

Dr Sid Ahmed Kherraf of Pfizer Inc. coordinated the expert panel meeting. Editorial and writing support was provided by Ms Lianne Cowie and Mr Andy Lee of MIMS (Hong Kong) Limited and was funded by Pfizer. Pfizer provided an unrestricted educational grant but did not write or control the scientific content of the manuscript.

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Appendices

Appendix A - English DN4 questionnaire (29)

DN4 Questionnaire

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT

Question 1: Does the pain have one or more of the following characteristics?
1 - Burning
2 - Painful cold
3 - Electric Shocks

Question 2: Is the pain associated with one or more of the following symptoms in the same area?
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 may reveal one or more of the following characteristics?
8 - Hypoesthesia to touch
9 - Hypoesthesia to prick

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

This can also be found in pdf format at:
http://www.mejfm.com/June%202017/Neuropathy%20Appendix1.pdf
Appendix B - French DN4 questionnaire (29)

Questionnaire DN4

Répondez aux 4 questions ci-dessous en cochant une seule case pour chaque item.

INTERROGATOIRE DU PATIENT

Question 1: La douleur présente-t-elle une ou plusieurs des caractéristiques suivantes?

1 - Brûlure
2 - Sensation de froid douloureux
3 - Décharges électriques

Question 2: La douleur est-elle associée dans la même région à un ou plusieurs des symptômes suivants?

4 - Fourmillements
5 - Picotements
6 - Engourdissement
7 - Démangeaisons

EXAMEN DU PATIENT

Question 3: La douleur est-elle localisée dans un territoire ou l'examen met en évidence?

8 - Hypoesthésie au tact
9 - Hypoesthésie à la piqûre

Question 4: La douleur est-elle provoquée ou augmentée par:

10 - Le frottement

This can also be found in pdf format at:
http://www.mejfm.com/June%202017/Appendix2.pdf
Appendix C - Arabic DN4 questionnaire (30)

This can also be found in pdf format at:
http://www.mejfm.com/June%202017/Appendix2.pdf