

COMPREHENSIVE ASSESSMENT AND PHARMACOTHERAPY OF PATIENTS WITH CHRONIC PAIN SYNDROME DUE TO DIABETIC NEUROPATHY AND POSTHERPETIC NEURALGIA

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ABSTRACT

Management of chronic pain, usually associated with comorbid conditions, remains challenging. General practitioners, together with multidisciplinary teams of specialists, play an important role in diagnosing and treating patients with chronic pain of different origin. This article outlines the main mechanisms underlying chronic nociceptive and neuropathic pain and describes some helpful techniques to initially evaluate and regularly monitor pain. Pharmacologic treatment options, including their benefits and adverse effects, with particular emphasis on the management of diabetic neuropathy and postherpetic neuralgia, commonly seen in the primary care practice setting, are presented.

Chronic pain, regardless of its cause, is a disease syndrome and, as such, requires a comprehensive, individualised approach to each patient reaching beyond symptom control. Collaboration of physicians (general practitioners, diabetologists, neurologists, and pain specialists), pharmacists, and nurses in the management of patients with diabetic neuropathy and postherpetic neuralgia improves patient safety and contributes to better adherence to therapeutic regimens, which leads to more favourable outcomes and improved quality of life.

Keywords: Chronic pain, diabetic neuropathy, postherpetic neuralgia (PHN), pharmacotherapy, patient management.

INTRODUCTION

Pain is a physiological part of the protective mechanism that allows individuals to survive. In fact, pain evaluation is so important that it has been called the fifth vital sign that needs to be monitored on a regular basis, alongside pulse rate, arterial blood pressure, respiratory rate, and body temperature.^{1,2} Since the perception of pain is subjective, there is no particular objective test that can accurately measure the type and intensity of pain experienced by a patient. Therefore, patient self-reporting is usually considered to be a key component of pain evaluation.^{1,2} However, these reports must be linked with a detailed medical interview, physical examination, laboratory and imaging test results, as well as with patient scores on standard pain scales.¹ Also, chronic pain needs to

be evaluated at regular intervals of time and should be precisely documented in the patient's records to ensure that every member of the treatment team, including general practitioners (GPs), consulting specialists (diabetologists, neurologists, or pain specialists), pharmacists, nurses, rehabilitation therapists, or other providers, has access to current information, which will allow precise monitoring of the patient's response to treatment.^{1,3}

In contrast to acute pain evaluation, which is often brief and direct, assessment of chronic pain (nociceptive or neuropathic), particularly if it is combined with different comorbid conditions or remains refractory to standard initial treatment, is very complex. The International Association for the Study of Pain (IASP) defines neuropathic pain as "a pain arising as a direct consequence of

a lesion or disease affecting the somatosensory system".² Assessment of neuropathic pain requires multidisciplinary knowledge and experience, co-operation within a treatment team, and a professional relationship with each patient based on mutual trust and respect. Many GPs are in a unique position to establish long-term relationships with their patients that facilitate good communication.^{1,3}

INITIAL ASSESSMENT OF PATIENT SUFFERING FROM CHRONIC PAIN

Initial assessment of every patient suffering from chronic pain is focussed on obtaining a detailed history covering basic characteristics of the patient's pain, such as its type (nociceptive versus neuropathic), localisation, frequency, duration, and aggravating and alleviating factors.^{1,3} In addition, it is crucial to briefly analyse some other related domains of the patient's life, including his/her physical and psychosocial wellbeing (including family and occupational situation), functional status, comorbidities, mental and emotional status, present or past psychiatric disorders, and current or past substance abuse problems.^{1,3}

The physical exam should be focussed on musculoskeletal and neurological systems. Diagnostic studies need to be analysed in comparison to past medical records, if available. A goal of such a comprehensive assessment is a correct diagnosis and a reasonable management plan. It should be emphasised that simple steps, including obtaining a patient's detailed history and performing a thorough physical exam, are often instrumental for detecting potential causes of a patient's pain.^{1,3} At this point, knowing the right questions to ask can lead to finding the root cause(s) of the patient's pain, indicating further appropriate directions for diagnosis and treatment. There are several questions that are particularly helpful at the beginning of diagnostic work-up:

- Using a body diagram (front and back), can you point to the exact site of your pain?
- Does your pain spread or radiate? Where?
- What things relieve or worsen it?
- When did the pain begin?
- What was done about it?
- Have you been using any medications or procedures? What kind?
- Did any of those interventions work?
- What medications (over-the-counter or prescription), vitamins, or dietary supplements, are you currently taking?

- Do you drink alcohol?
- Do you smoke?
- Do you use any drugs?

These direct questions, in addition to obtaining precise characteristics of the pain, can also determine whether there are any psychosocial issues that might interfere with a future therapy plan.^{1,3} As mentioned before, the physical exam is an integral component of the comprehensive pain assessment. In addition to taking vital signs, it should include evaluation of mental status and mood, posture (e.g. guarding or splinting), neurological status (e.g. sensory or motor dysfunctions), and signs of sympathetic dysfunction or musculoskeletal abnormalities.^{1,3}

In general, laboratory and radiographic evaluations are performed in cases in which previous evaluations were inadequate or the patient's quantity or quality of pain has changed.^{1,3} Although the experience of pain is subjective, several validated instruments exist, including both one-dimensional and multi-dimensional questionnaires that are designed to help measure the intensity and type of the patient's pain. Since chronic pain requires regular monitoring, any chosen evaluation method, depending on the patient's age and communication/language skills, needs to be used consistently during each follow-up visit.^{1,4}

Typical one-dimensional pain scales that are most useful in a daily practice include:

- The Numeric Rating Scale (NRS): the patient rates his/her pain intensity on a scale of 0 (no pain) to 10 (worst imaginable pain). Patients may also use the scale at home to record pain intensity at different times in relation to their activity levels and applied treatments, which should be documented in a pain journal. This kind of documentation is very helpful in determining pain patterns.^{1,4}
- The Visual Analogue Scale (VAS): allows a more descriptive rating of pain, since the patient marks the line at the point between 0 and 10 that best describes his/her pain intensity.^{1,4}
- The Wong-Baker FACES[®] pain rating scale: uses facial expressions to depict different degrees of pain intensity. It is particularly useful for assessing children and cognitively impaired or elderly patients (who often have some language barriers or difficulty communicating verbally).^{1,4}
- The Verbal Rating Scale (VRS).^{1,4}

Some other validated, multi-dimensional pain assessment tools include:

- The McGill Pain Questionnaire (MPQ): covers three dimensions of pain: sensory, affective, and evaluative. The patient selects words that best describe the quality of their pain from a pre-defined list, such as burning, shooting, throbbing, aching, and pins and needles.⁵
- The Brief Pain Inventory-Short Form (BPI-SF), a nine-item self-report questionnaire (scored on a 0-10 scale), examines pain severity and its interference with emotional and physical functioning. For the BPI-SF, the arithmetic mean of four pain severity items yields a general pain severity score; the mean of seven interference values yields a general interference score and other items inform about the pain location and the use of pain relief strategies.⁶
- The Douleur Neuropathique 4 (DN4) questionnaire: a tool aimed at screening neuropathic pain that is used to help distinguish between neuropathic and nociceptive pain. It is made up of seven items related to pain symptoms and three items related to physical evaluation. DN4 is correlated with the medical diagnosis.⁷

These tools can provide a comprehensive profile of the patient's pain, whilst also taking into consideration emotional distress, and the degree to which the individual can function in various domains of life. In addition, several multi-dimensional tools exist, for example the Neuropathic Pain Scale (NPS), Treatment Outcomes of Pain Survey (TOPS), and the Oswestry Disability Index (ODI). These can be used to assess specific types of pain or to assess pain in terms of functional status among large groups of patients. However, these tools are usually reserved for the research setting.^{1,4}

NOCICEPTIVE PAIN PATHWAY

In order to better understand the development of two main types of pain, nociceptive and neuropathic, with their respective specific symptoms commonly experienced by patients, it is important to briefly review the normal anatomy and physiology of pain pathways. Nociceptive pain pathways allow individuals to perceive pain and avoid further injury after a noxious stimulus, such as heat, cold, or mechanical trauma activates receptors in tissues (e.g. skin). This noxious stimulus is then transduced into incoming signals that travel toward the central nervous system along small, unmyelinated C fibres.

The C fibres make synaptic connections in the dorsal horn of the spinal cord. The second-order neurons cross the midline and travel up the contralateral spinal tract to the thalamus and other parts of the brain so that the pain sensation can be perceived.^{1,4} It should be emphasised that the intensity of the incoming noxious signals can be modulated by a descending inhibitory tract. For instance, opioids bind to specific receptors in the brain and cause an increase in descending inhibition, to reduce the incoming pain signals. This, in turn, allows patients to decrease the degree of pain that they feel.^{1,4}

ALLODYNIA AND HYPERALGESIA

The normal anatomy and physiology of a pain pathway can be depicted as the stimulus intensity increasing from a light touch to a pinch causing a person to start perceiving pain, which can be rated in intensity on a numeric scale from 0-10. At this point, injured tissues become sensitised, and the pain perception is often greater.^{1,4} For example, upon a non-painful stimulus, such as a light touch, the injured area can cause a mild-to-moderate pain sensation called allodynia. Similarly, a mildly painful stimulus, such as a light pinch, may cause in these circumstances severe pain, called hyperalgesia. This response is normal to ensure protection of the injured area until it heals. However, persistence of the allodynia and hyperalgesia after the tissue injury has healed is characteristic of neuropathic pain.^{2,4}

NEUROPATHIC PAIN PATHWAY

The management of chronic neuropathic pain, whether peripheral or central, is clinically challenging and often frustrating because of the complex pathophysiology of neuropathic pain transmission.^{2,4} Neuropathic pain is a common form of chronic pain, which results from damage to the peripheral nervous system, often due to diabetic neuropathy, postherpetic neuralgia (PHN), or chronic lumbar radiculopathy.^{1,4} In addition, neuropathic pain can also be caused by injury to the central nervous system, which can occur in: stroke, spinal cord injury, and multiple sclerosis (MS).^{1,4}

In general, symptoms of neuropathy can be categorised as:^{2,8}

- Negative, resulting in partial or total loss of sensation
- Positive, including various types of abnormal or unpleasant sensations (due to normal stimuli), such as:

- Dysaesthesia: burning/stabbing
- Paraesthesia: tingling or prickling (pins and needles)
- Allodynia: painful sensation due to a mild stimulus; not normally associated with pain
- Hyperalgesia: exaggerated response to painful stimulus

CAUSES, MECHANISMS, AND SYMPTOMS OF NEUROPATHIC PAIN

Neuropathic pain represents a chronic condition that is often difficult to diagnose and to treat due to complex interrelations between the causes, mechanisms, and symptoms of various diseases underlying this type of pain.^{2,8} In neuropathic pain, neurons in the spinal cord often become hyper-responsive, leading to excessive pain sensation (hypersensitivity) and extension of pain beyond the region of original damage due to injury or disease. Moreover, changes in sodium and potassium channels after a nerve injury increase cell membrane excitability and cause paraesthesias.⁸ The sensitisation of both central and peripheral neurons alters perception of pain and increases sensitivity to temperature and to touch. Peripheral nerve injury may also reduce inhibitory cerebral influence on dorsal horn neurons.^{1,8}

DISTAL SYMMETRIC POLYNEUROPATHY

Distal symmetric polyneuropathy (DSPN) is the presence of symptoms and signs of peripheral nerve dysfunction in patients with diabetes (after the exclusion of other causes). DSPN has a multifactorial pathogenesis (e.g. oxidative and inflammatory stress associated with metabolic disorders) and is the most common diabetic neuropathy. DSPN that involves small-diameter Type A delta and Type C sensory fibres usually results in symptoms such as painful paraesthesia, which is perceived as burning, stabbing, crushing, cramping, or aching sensations (often aggravated at night).⁹ These symptoms typically develop in the hands in a glove-like distribution. In addition, paraesthesias and the loss of sensation in the feet, in a sock-like distribution, creates a risk of developing foot ulcers that can be complicated by gangrene.⁹ Moreover, frequently coinciding decreased ankle and knee reflexes, weakness of foot muscles, and impaired proprioception can affect the gait, and cause sensory ataxia. Furthermore, many patients experience symptoms related to the autonomic nervous system, such as resting

tachycardia, orthostatic hypotension, bladder or bowel dysfunction, anhidrosis, and sluggish reaction of pupils to light.⁹

A neurologic evaluation is necessary to determine severity and to rule out other causes of neuropathy. Management of each diabetic patient with DSPN, in addition to his/her appropriate blood glucose levels, lipid levels, and blood pressure control, needs to take into consideration any medical or mental comorbidities, possible treatment side effects, and some other individual factors (e.g. socio-economic).

PHARMACOTHERAPY FOR DIABETIC NEUROPATHY

Pharmacotherapy for diabetic neuropathy includes various medications from the following groups:^{9,10}

- Antidepressants
 - Tricyclic (e.g. amitriptyline, imipramine, desipramine)¹¹
 - Selective serotonin/norepinephrine reuptake inhibitors (SNRIs) (e.g. duloxetine, venlafaxine)
 - Selective serotonin reuptake inhibitors (e.g. paroxetine, citalopram)
- Anticonvulsants (e.g. gabapentin, pregabalin, sodium valproate, phenytoin, carbamazepine)
- Non-steroidal anti-inflammatory drugs (e.g. ibuprofen, naproxen)
- Analgesics
 - Topical (e.g. lidocaine gel [5%], capsaicin)
 - Opioids (e.g. tramadol, morphine sulfate, or oxycodone). It should be emphasised that add-on therapy with opioids may be necessary in some patients, who failed to respond to other treatments; however, in such cases, a referral to specialised pain clinics and close medical supervision are recommended).

A choice of medication from any of these groups (or combination therapy) for the management of diabetic neuropathy should be made after considering the individual patient's clinical status, goals, and needs.^{9,10} Unfortunately, adverse effects of these medications (see next section) are common, and thus the GP's familiarity with the most typical side effects is important in order to achieve realistic treatment goals whilst maintaining the patient's comfort. In addition, educating the patients about some of the possible adverse effects of the otherwise beneficial therapy may help

them to be more motivated and adherent to the treatment regimen.^{10,12}

POSSIBLE ADVERSE EFFECTS OF MEDICATIONS USED IN TREATMENT OF DIABETIC NEUROPATHY

In general, the anticonvulsants and antidepressants commonly used for the treatment of DSPN decrease neuronal excitability, leading to a reduction of pain. However, they are not free of adverse effects.¹¹ Second-generation anticonvulsants (e.g. gabapentin, pregabalin) can cause somnolence, dizziness, fatigue, headache, confusion, diarrhoea, nausea, weight gain, peripheral oedema, and thrombocytopenia/neutropenia.¹² First-generation anticonvulsants (e.g. sodium valproate) can cause tremors, hepatotoxicity, peripheral oedema, weight gain, hair loss, pancreatitis, and interactions with tricyclic antidepressants.¹² SNRIs (e.g. venlafaxine, duloxetine) can cause poor appetite, weight loss, insomnia, drowsiness, dizziness, fatigue, headache, mydriasis, nausea/vomiting, and urinary retention.¹² Tricyclic antidepressants (e.g. nortriptyline, amitriptyline) can cause dry mouth, constipation, blurred vision, dizziness, drowsiness, and increased heart rate.¹²

ADDITIONAL MEDICATIONS BEING CONSIDERED FOR NEUROPATHIC PAIN

Current recommendations of the American Diabetes Association (ADA) are designed to help primary care physicians focus on effective management of neuropathies in patients with Type 2 diabetes mellitus (T2DM).¹³ In addition to recently completed or ongoing clinical trials in the area of diabetic neuropathy, investigating SNRIs (e.g. duloxetine) or anticonvulsants (e.g. pregabalin) in different diabetic populations, there is still a growing need to find more effective therapeutic approaches to DSPN that are less toxic. Some of them are briefly described below.

Alpha-Lipoic Acid

Alpha-lipoic acid (ALA) is an antioxidant that, according to a multicentre placebo-controlled trial, was found to cause short-term symptomatic relief of neuropathy symptoms in patients with T2DM (its recommended dose is 600 mg/day for 3 weeks).¹⁴

Actovegin

Actovegin is a deproteinised derivative of calf blood, containing inorganic substances (electrolytes and

trace elements), organic components (amino acids, oligopeptides, nucleosides, and glycosphingolipids), and inositol phospho-oligosaccharides that may enhance insulin actions (central or peripheral). Based on the randomised clinical trial by Ziegler et al.,¹⁵ it was found that upon therapy with actovegin (e.g. intravenous [2,000 mg/day], and then oral [1,800 mg/day] administration over 5 months) both sensory functions and quality of life of patients with T2DM and polyneuropathy were improved.

Aldose Reductase Inhibitors

Aldose reductase inhibitors (e.g. alrestatin, sorbinil, tolrestat, and epalrestat) block the rate-limiting enzyme in the polyol pathway, which is activated by hyperglycaemia. However, these medications are not currently US Food and Drug Administration (FDA) approved. Epalrestat, which reduces intracellular sorbitol accumulation, has been shown to improve motor and sensory nerve conduction as well as diabetic neuropathy symptoms (e.g. pain, hyperaesthesia, numbness, coldness of extremities, dizziness, and orthostatic fainting) compared to baseline or placebo. At present, epalrestat is marketed only in Japan and its recommended dose is 150 mg/day for 12 weeks.¹⁶

POSTHERPETIC NEURALGIA

Brief Aetiology and Clinical Manifestations of Herpes Zoster

Herpes zoster (or shingles) reflects the reactivation of the varicella-zoster virus. After the primary varicella infection (chickenpox), the virus remains quiescent in the dorsal root ganglia, often for many decades, kept in check by the normal immune system.^{17,18} However, with ageing, or due to immunosuppression associated with illness, the virus can multiply.

The clinical manifestations of herpes zoster can be divided into three phases:

- Pre-eruptive or preherpetic neuralgia
- Acute eruptive phase: unilateral patchy erythema, herpetiform vesicles that rupture, crust, and involute, and severe pain (acute herpetic neuralgia)
- Chronic or post-herpetic neuralgia^{17,18}

When the pain associated with an acute herpes zoster outbreak persists for more than 2 months, it is called PHN, which is caused by viral-mediated damage to peripheral afferent neurons. Immediate

treatment with antiviral medications can reduce the severity of zoster and the risk of future PHN. However, this neuralgia may persist for a few years.^{17,18}

The pain of PHN is usually severe and is often characterised by constant aching or burning, electric shock-like sensation, allodynia, and hyperalgesia.^{17,18}

Treatment of Postherpetic Neuralgia

The recommended medications, used to treat PHN include:^{17,18}

- Antidepressants (tricyclic): nortriptyline (which has fewer cardiac side effects), desipramine, amitriptyline
- Anticonvulsants: gabapentin, pregabalin
- Opioids (only in selected, severe cases; during acute phase of herpes zoster)
- Lidocaine topical preparations
- Capsaicin topical preparations

The adverse effects of medications used in the therapy of PHN and diabetic neuropathy are identical. Similarly, the side effects of lidocaine and capsaicin topical preparations, used in the management of both of these conditions, may include abnormal skin sensations (e.g. burning or change in hot or cold sensation), redness, or swelling at the application site.^{17,18} Since there is only limited evidence to guide the selection of different pharmaceutical agents, the adverse effects of these medications should help with choosing the most appropriate and available agent by considering the benefits and risks for each individual patient. Furthermore, the FDA has approved a live attenuated varicella-zoster virus vaccine, Zostavax®, that has been used since 2006, and has

demonstrated a decrease in the incidence rate of herpes zoster. Zostavax reduces the risk of developing shingles by 51%, and PHN by 67%. It is administered in one dose injection. Currently, Zostavax is approved for use in patients >50 years old, and is considered to be cost-effective.¹⁹

SUMMARY

Pain assessment is one of the competencies that GPs need to master in order to correctly diagnose and effectively treat patients with chronic pain of different origin. In many cases, chronic pain can be alleviated, at least to some degree, with appropriately targeted therapeutic options, even if the patient may have to try several different modalities before finding one that works best. In clinical practice, two main categories of chronic pain, neuropathic and nociceptive, often overlap. Moreover, many medical comorbidities, mental disorders, stress, or environmental factors (at work and at home) can complicate the management of chronic pain. For these reasons, chronic pain as a disease syndrome, should be addressed within a biopsychosocial, interdisciplinary model of care, which considers each patient's psychosomatic, occupational, environmental, family, and social conditions. Finally, it should be emphasised that a team collaboration between physicians (e.g. GPs, diabetologists, neurologists, psychiatrists, rehabilitation, and pain specialists), pharmacists, and nurses who manage patients with diabetic neuropathy and PHN improves patient safety and contributes to better adherence to medical regimens. This, in turn, leads to more favourable outcomes and better quality of life.

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