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Current Concepts in Physiatric Pain Management

Assessing and Treating Patients With Neuropathic Pain

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Abstract

Neuropathic pain (NP) is a significant source of suffering, disability, and impairment, as well as an enormous cost to society. Historically, pharmacologic treatment has been limited to drugs approved for other conditions, including anticonvulsants, antidepressants, antiarrhythmics, and opioids, but in the past 2 decades several drugs have been approved by the Food and Drug Administration specifically for NP. Understanding the underlying pathophysiology and clinical presentation of the various causes of NP states facilitates a rational selection of pharmacologic, interventional, rehabilitative, and psychological options for reducing pain and maximizing function.

Introduction

Chronic neuropathic pain (NP) is the result of direct central or peripheral nerve damage. Estimates of the prevalence of this condition range from 2% to 40% of all adults [1-15], and there are an estimated 3.75 million cases of chronic NP in the United States [16]. The most commonly studied and best understood causes are NP associated with diabetes mellitus [17-23] and herpes zoster [24-28], but many other clinically important causes exist, including cancer-associated pain, spinal cord injury, phantom pain [16], radiculopathy [11,29], complex regional pain syndrome (CRPS), poststroke pain, and other painful peripheral neuropathies or injuries. Regardless of the cause, NP often causes significant impairments that limit activity and restrict participation at the community level, resulting in increased health care expenditures, decreased quality of life, and lost productivity.

Pain is classically categorized as either nociceptive or neuropathic. Nociceptive pain is defined by the International Association for the Study of Pain as pain that "arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors" [30]. Examples of nociceptive pain include postoperative pain that is acute in onset and of relatively short duration [31-35] and arthritis, which is more chronic in nature. NP is caused by a lesion or disease of the somatosensory nervous system and may occur in the periphery (eg, compressive neuropathies) or centrally (eg, stroke) [31]. Although acute nociceptive pain can usually be treated successfully with opioid or nonsteroidal anti-inflammatory analgesic agents, NP is less responsive to these drugs [33,34,36]. Instead, the preferred agents for controlling NP include antiseizure medications that stabilize nervous system activity, antidepressants that modulate circulating neurotransmitters, or antiarrhythmic agents that block sodium channels [33,37].

Evidence-based treatment of NP is difficult because few prospective randomized controlled trials pertaining to the medications, procedures, rehabilitation approaches, and psychological interventions most commonly used in clinical practice have been published. At this time, the only Food and Drug Administration (FDA) approved medications for the treatment of NP are carbamazepine [38] (trigeminal neuralgia); lidocaine patch 5% [39] (postherpetic neuralgia); gabapentin [40], including long-acting formulations [41,42] (postherpetic neuralgia); pregabalin [43] (postherpetic neuralgia, diabetic peripheral neuropathy, and NP associated with spinal cord injury pain); capsaicin [44] (postherpetic neuralgia); duloxetine [45] (diabetic peripheral neuropathy); and extended-release tapentadol [46] (diabetic peripheral neuropathy). Various opioids have been approved by the FDA for chronic pain, but not specifically for NP. Off-label use of agents indicated for depression, seizures, and cardiac arrhythmias is common [17,28,33,37,47-49], but because evidence for their safety and efficacy is lacking, formal guidelines for their use are not available.

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A rational approach to the treatment of NP requires categorizing the signs and symptoms according to the underlying pathophysiologic mechanism so that drugs may be chosen that target those mechanisms rather than classifying and treating patients based solely on a diagnosis, as has traditionally been done [50]. Choosing effective treatments based on a given diagnosis can be challenging and produces poor outcomes because a single diagnosis may present differently in different patients, the diagnosis may have multiple underlying mechanisms of pain, and/or these mechanisms may change over time. Targeting treatment to symptoms and signs will theoretically result in more effective therapy, improved functional status, and improved quality of life.

The purpose of this article is to review the evaluation, diagnosis, and pharmacologic treatment of NP based on the underlying pathophysiology, as well as the nonpharmacologic therapeutic options available to optimize functional restoration and quality of life.

Method of Literature Selection

Relevant publications were identified through Medline searches (1950-2015), examination of relevant published articles and book chapters, and personal knowledge of the authors. Studies included for review were those that (1) elucidate or describe the mechanisms of NP, (2) provide evidence for the evaluation of NP, (3) investigate oral or topical pharmaceutical agents or interventional therapies for NP in adults, or (4) describe physical therapy, occupational therapy, or psychological treatment options for chronic NP. Studies in pediatric populations were excluded.

Evidence

Types of Neuropathic Pain

Physiologically, NP results from central and/or peripheral nervous system damage or dysfunction [2,51,52]. Logically, such nervous system damage is expected to result in sensory loss (negative symptoms), but in clinical practice, some patients present with pain and/or abnormal sensations (positive symptoms) [16]. When they are unpleasant, these abnormal sensations are termed *dysesthesias*, and when they are not unpleasant, they are classified as *paresthesias* [31]. The positive symptoms associated with NP syndromes can broadly be classified as stimulus-evoked pain that presents with hyperalgesia and/or allodynia or stimulus-independent pain (ie, spontaneous pain) that is often described as shooting, stabbing, or burning and may be further classified as persistent or paroxysmal (Figure 1).

Symptoms and Mechanisms of Neuropathic Pain

Stimulus-Evoked Pain: Hyperalgesia and Allodynia

Two specific examples of dysesthesias are hyperalgesia, which is an exaggerated or increased response to a normally painful stimulus (eg, a pinprick), and allodynia, which is pain produced by a typically nonpainful stimulus (eg, light touch) [32]. The underlying mechanisms of stimulus-evoked pain can be divided into peripheral processes such as peripheral sensitization and central processes including central sensitization and disinhibition.

Peripheral sensitization is a process in which peripheral primary afferent nerve terminals (Aδ and C fibers), which are normally responsible for the transduction of noxious mechanical, chemical/inflammatory, or thermal stimuli into action potentials, become hyperexcitable. The mechanism by which this effect occurs involves inflammatory mediators including bradykinin, histamine, prostaglandins, cytokines, and substance P released from injured tissue [53] that act to lower the threshold or increase the gain of the inflammatory milieu, thus enhancing the chance that an action potential is transmitted by the primary afferent nociceptors to the central nervous system.

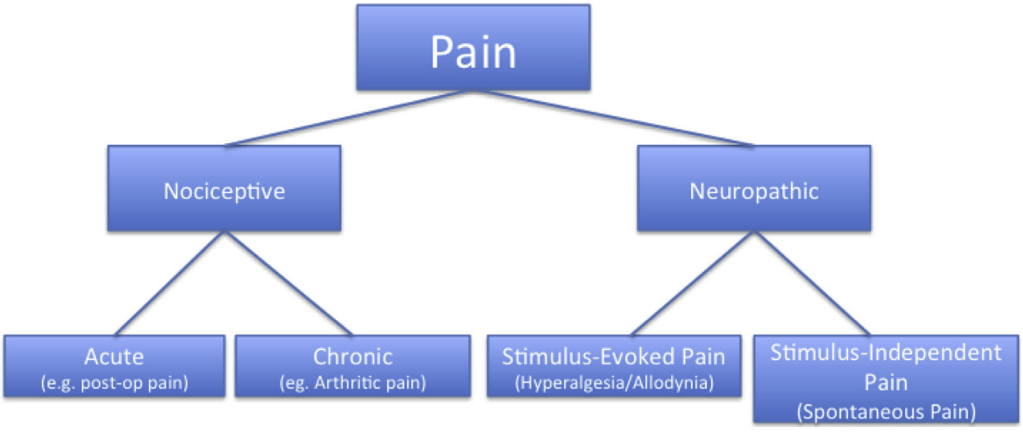

Figure 1. Classification of pain.