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REVIEW

TRANSLATIONAL NEUROPATHIC PAIN RESEARCH: A CLINICAL PERSPECTIVE

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Abstract—Neuropathic pain encompasses a broad range of conditions associated with a lesion or disease of the peripheral or central somatosensory system and its prevalence in the general population may be as high as 7–8%. The interest in the pathophysiology of neuropathic pain has increased over the last two decades with an exponential increase in the number of experimental studies. However, despite the hopes raised by scientific discoveries, there has been no rational development of a truly new class of drugs. This situation revealing the limitations of certain experimental models, also results of limitations in clinical research. One of the reasons for the therapeutic difficulties in these patients is probably due to the fact that treatments are used in a uniform fashion whatever the clinical picture, while these syndromes are in fact highly heterogeneous. Clinical advances have recently been made in this field, following the validation of new specific clinical tools and the standardization of quantitative sensory testing paradigms facilitating improvements in the clinical characterization of these syndromes. It has been clearly demonstrated that neuropathic pain is a consistent clinical entity, but it is multidimensional in terms of its clinical expression, with different sensory profiles, potentially reflecting specific pathophysiological mechanisms. This new conceptualization of neuropathic pain should improve the characterization of the responder profiles in clinical trials and provide valuable information for the development of new and more clinically sound translational approaches in experimental models in animals.

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Key words: chronic pain, clinical research, translational research, treatment strategies.

Contents

INTRODUCTION

Chronic pain affects at least 20–30% of the general population (Elliott et al., 1999; Bouhassira et al., 2008). It is still essentially managed according to the empirical classification established more than 60 years ago, in which three major categories of pain syndromes can be distinguished: (i) nociceptive pain of various causes (e.g. burns, trauma, infections, tumors, surgery), which may affect various tissues (skin, joints, muscles, viscera). This type of pain is usually associated with inflammatory processes and is treated with usual analgesics, such as anti-inflammatory agents and weak or strong opioids; (ii) neuropathic pain syndromes, which are related to peripheral or central nervous system injuries. These chronic and extremely incapacitating pain syndromes (Attal et al., 2011a,b) are among the most difficult to treat because they do not respond to usual analgesics and respond only partially to antidepressants, antiepileptic drugs or strong opioids; (iii) 'dysfunctional', or 'primary' pain which remains ill-defined and includes various chronic pain syndromes, such as irritable bowel syndrome and fibromyalgia, not associated with an identifiable somatic, visceral or neurological lesion (Treede et al., 2015). The treatment of chronic pain syndromes remains a major clinical challenge, as pain relief is generally only partial and achieved in less than 50% of patients on currently recommended treatments; success rate are particularly low for patients with neuropathic pain (Finnerup et al., 2015).

Interest in neuropathic pain syndromes has increased over the last two decades, with a large proportion of experimental and clinical studies devoted to the investigation of their mechanisms and the improvement

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of treatment outcomes. The multiple (>20) animal models now available have considerably modified our understanding of the pathophysiological concepts relating to neuropathic pain. However, it remains unclear whether the mechanisms identified in these models actually operate in clinical pain conditions, as only a few such mechanisms have been directly demonstrated in patients. The exponential increase in the number of experimental studies conducted over the last 15 years in the field of neuropathic pain has not yet led to any major clinical applications. Thus, although classical first line neuropathic pain treatments (i.e. antidepressants and anticonvulsants) are now more widely and better used than in the past, there has been no rational development of a truly new class of drugs, despite the hopes raised by scientific discoveries and the considerable investment in this area by many public and private laboratories. One reason for this may be the poor predictive value of pharmacological data for new potential analgesics developed in animals (Percie du Sert and Rice, 2014). These experimental models, which have been shown to be highly sensitive to many current or new pharmacological agents, unfortunately seem to lack specificity for the identification of new compounds of potential clinical relevance. We feel that this situation, revealing the limitations and unsuitability of certain experimental models, also results from a lack of interaction between clinicians and basic scientists and a lack of pathophysiological studies carried out directly on patients. Indeed, a clinical approach of this type appears to be essential for the formulation of new relevant scientific questions, the adaptation of experimental models, the confirmation of pathophysiological hypotheses and the establishment of links between clinical questions and basic research findings. The fascinating and highly promising findings and hypotheses continually generated by basic scientists, as a result of the extraordinary technological developments occurring in molecular and cell biology, have probably overshadowed the lack of basic clinical information. It therefore remains uncertain whether further technological progress and the application of increasingly sophisticated methods based on current experimental models can make a significant contribution to therapeutic applications in this field, unless the clinical landscape is clarified.

In this review we will summarize the main clinical aspects on the definition, diagnosis, assessment and pharmacological management of neuropathic pain in the clinical setting. We will then address specific issues relating to clinical research in this field, including possible changes to the design of future clinical trials, that might facilitate translational research in the future.

GENERAL CLINICAL CHARACTERISTICS OF NEUROPATHIC PAIN

According to the definition proposed by the International Association for the Study of Pain (IASP) the term neuropathic pain (NeP) refers to *pain caused by a lesion or disease of the somatosensory system*. Thus, neuropathic pain syndromes encompass a very large number of etiologies and, unsurprisingly, epidemiological studies have shown that their prevalence in the general population may be as high as 7 to 8% (Torrance et al., 2006; Bouhassira et al., 2008), accounting for 20 to 25% of those with chronic pain.

Clinical manifestations include both positive and negative phenomena (Baron et al., 2010). The positive phenomena include various painful symptoms (see below), *paresthesia* and/or *dysesthesia,* which, by definition, are abnormal *nonpainful* sensations (e.g. tingling, numbness, pins and needles). Negative phenomena usually include neurological sensory deficits in the painful area, together with other deficits (motor, cognitive etc.), depending on the location of the lesion. Such symptoms have been reported for a number of lesions or diseases affecting the peripheral or central nervous system. Painful peripheral neuropathies include multiple conditions, such as diabetic neuropathy, post-herpetic neuralgia, traumatic or post-surgical nerve injury and HIV neuropathy. Many patients present with mixed pain syndromes involving both neuropathic and non-neuropathic mechanisms, such as lumbar or cervical radiculopathies, which are among the most frequent causes of peripheral neuropathic pain in the general population (Bouhassira et al., 2008). Central pain syndromes are not uncommon, as they are observed in up to 8% of patients after a stroke, in approximately 30–50% of patients with a spinal cord injury, a large majority of whom present with a syringomyelia, and up to 20–25% of patients with multiple sclerosis (Klit et al., 2009; Finnerup and Baastrup, 2012; Foley et al., 2013).

Neuropathic pain symptoms include spontaneous pain, continuous or paroxysmal and evoked pain (Baron et al., 2010). Evoked pain, which can be more distressing than spontaneous pain, is termed *allodynia* when it is triggered by normally non-noxious stimuli and *hyperalgesia* when it corresponds to an exaggerated response to a normally noxious stimulus. Evoked pain can be triggered by mechanical or thermal stimuli. Mechanical allodynia can be preferentially triggered by moving stimuli (i.e. *dynamic* mechano-allodynia), or by pressure or punctate stimuli (i.e. *static* mechano-allodynia). Evoked pain can also be triggered by thermal stimuli, either heat or cold, but cold allodynia/hyperalgesia is much more frequent than heat allodynia/hyperalgesia in these patients (Attal et al., 2008; Maier et al., 2011).

It has repeatedly been shown over the last 10 years that the words that patients used to describe their pain (i.e. pain descriptors) differ between patients with neuropathic and non-neuropathic pain. Indeed, despite its many causes, neuropathic pain is characterized by the combination of a relatively small number of ‘‘core” pain qualities (particularly burning pain, electric shock-like pain, dysesthesia and brush allodynia) that distinguish it from other types of chronic pain (Bouhassira and Attal, 2011). This observation has led to the development and validation of a number of clinical tools in the form of simple symptom-based questionnaires for the screening and identification of neuropathic pain in clinical practice (e.g. Bennett, 2001; Bouhassira et al., 2005; Freynhagen et al., 2006). None of the individual

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