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Short Review

Chronic Non-Cancer Pain: New Definitions, New Paradigms and Old Myths

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Abstract

Chronic pain is a high prevalent phenomenon that involves biological, psychological, and social aspects with negative effects on function, mood, and quality of life. The International Association for the Study of Pain (IASP) advocates updating the current definition of chronic pain to better recognize the diversity and complexity that is difficult to capture in a brief definition. Treatment of chronic pain is still a challenge so that two-thirds of patients report an unsatisfactory level of pain control with currents approaches.

This article discusses the features characterizing chronic pain towards new definitions and treatment paradigms while challenging existing myths and considers the obstacles to achieving a satisfactory level of pain control. It highlights the literature's criticisms of a unimodal approach to chronic pain and supports a multimodal (pharmacological and non-pharmacological) and holistic strategy that comprises the intensity of pain, but also its pathophysiology, comorbidities, such as anxiety and depression, social context, and psychological aspects. Finally, concerns relating to the management of chronic non-cancer pain and the use of opioids are addressed. The good and the bad of opioids were discussed for a more responsible opioid-prescribing strategy in chronic pain basing on a strong clinical and educational component and a continuous monitoring of these patients both in primary care in specialized settings. Translating from a multidisciplinary approach to an interdisciplinary team approach will lead to an improved response to the needs of patients, providing a holistic strategy that accounts for the different pathogenesis of pain syndromes, their phenotypes, the nervous system involvement, and remodeling, and the biopsychosocial components of chronic pain.

Keywords: Analgesia; Chronic pain; Cognition; Myths; Non-cancer pain; Opioids; Physical health; Psychological health; Social relationships

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Introduction

Chronic pain is a complex phenomenon that involves biological, psychological, and social aspects. According to the latest definition of the International Association for the Study of Pain (IASP), it has been defined as "an unpleasant sensory and emotional experience associated with or resembling that associated with, actual or potential tissue damage or described by the patient in terms of such damage" [1]. The main aspect of chronic pain is that it persists beyond the normal tissue healing time [2], that is, more than 3 months, with negative effects on function, mood, and quality of life. The IASP suggests defining chronic pain as primary or secondary pain in disease or tissue damage cases, respectively unknown or known. This classification is strictly related to the pathogenesis of pain. Primary pain includes many pain syndromes, such as chronic widespread pain, visceral pain, orofacial pain, musculoskeletal pain, and complex regional pain syndrome, in which the pathogenesis is not well established [3]. Therefore, primary pain is also defined as nociplastic pain. Secondary pain includes pain syndromes with a defined nociceptive, inflammatory, neuropathic, or mixed pathogenesis [3].

The prevalence of chronic pain is extremely high; more than 116 million Americans have pain that persists for from weeks to a number of years [4] and between one-third and one-half of the population of the United Kingdom (in the order of 28 million adults) [5], while in Italy 26% of the population reported using drugs to treat chronic pain [6]. Moreover, it has a high socioeconomic impact, both in terms of individual and social aspects. A significant association between common chronic painful conditions and psychosocial aspects of life such as decreased working activity, reduced social relationships and impaired lifestyle has been reported [7]. In addition, the strong bidirectional association between anxiety, depression, and catastrophizing beliefs from one side and chronic pain from the other is well recognized [8]. According to a machine learning analysis of 118 patients with chronic pain compared with 86 healthy controls,

the most reliable features characterizing chronic pain were anxiety, depression, and belief of harm consequent to prolonged pharmacological treatments [9]. Finally, chronic pain frequently occurs with other comorbidities such as cardiovascular diseases and is closely linked with mortality [10]. These features can explain why adequate chronic pain treatment is often difficult to achieve, with two-thirds of patients reporting an unsatisfactory level of pain control with current treatments [8].

Challenging the Unimodal Approach to Chronic Pain Management

A new approach to chronic pain has begun to emerge in recent years since a unimodal approach (i.e., the pharmacological one) to chronic pain that considers only the physical aspect of pain and its intensity cannot adequately meet patients' needs. Nowadays, pain treatment should consider several aspects that comprise the intensity of pain, but also its pathophysiology, comorbidities such as anxiety, depression, and cognitive impairments, social context and psychological aspects. In this puzzling scenario, a multimodal approach that considers pharmacological and non-pharmacological ones (such as education therapies, psychological support, and physiotherapy) but also interventional techniques (such as infiltrative therapy and neuromodulation) has been proposed as the "trolley analgesic model" [11]. This novel dynamic model, as opposed to the historical World Health Organization (WHO) ladder, suggests choosing one or more drawers (each of one representing a different pain treatment), also together or in sequence, in order to manage the specific patient by a holistic approach and to assure a tailored, personalized treatment. This multimodal and holistic strategy to manage chronic pain patients should be followed in primary care [12] but also in specialized settings, as a recent Italian expert consensus has underlined [13].

Treatment of Non-Cancer Pain: Concerns and Strategies

However, several concerns remain regarding the management of chronic non-oncological pain, particularly on drug therapy. The previous Delphi survey [13] focused on the knowledge and prescriptive practice among pain specialists and other clinicians involved in pain management. It gave interesting insights on specific topics in pain management that are still controversial. One of the most important findings of this survey is that there is still a lack of consensus regarding opioid use in chronic non-oncological pain. Several reasons could explain these findings, such as the fear of the development of substance abuse disorder and the lack of knowledge of physiopathology of pain and available therapeutic strategies. The use, misuse, and abuse of opioids, with related adverse consequences till death, continue to have an escalating incidence [14]. The American Society of Interventional Pain Physicians has recently provided extensive guidelines on opioid prescribing and monitoring [15]. These guidelines still underline the importance of a comprehensive assessment of the patient's history, including physical, psychological, and social diagnosis, and establishing clear treatment goals (reduction of pain intensity and/or improvement of function by at least 30%). Only this strong alliance can assure an effective and responsible drug prescribing that must be followed by a continuous assessment of pain relief, functional status, adherence, side effects, and abuse risk. Clinicians must bear in mind that apart from most common side effects such as constipation, nausea, sedation and respiratory depression [16], other opioid-related adverse events have been reported, including opioid-induced androgen deficiency [17] and hyperalgesia [18], in addition to dependency and addiction. Several tools have been proposed to monitor patients on opioid therapy, such as the Opioid Risk Tool (ORT), which is a commonly used measure to estimate the risk of aberrant drug-related behaviors in patients with chronic pain who have been prescribed opioids [19], or the Routine Opioid Outcome Monitoring (ROOM), a computer-administered tool which includes domains including pain, mood, alcohol use, opioid use disorder and constipation [20].

Therefore, a responsible opioid-prescribing strategy requires a strong educational and clinical component [21] that starts from a careful assessment of all aspects of chronic pain but also considers the type of pain, its pathogenesis, and different mechanisms involved, such as glial contribution, peripheral and central sensitization and synaptic plasticity [22]. In fact, it is now well recognized that several mechanisms are involved in the development of chronic pain at many levels of both the peripheral and central nervous systems and that they are characterized by tremendous plasticity [23]. This more profound understanding of those pathways responsible for the induction and maintenance of chronic pain offers the opportunity for a precision medicine approach based on the subset of the pain phenotype. For example, a defined group of patients that exhibit central sensitization signs can be presumed to show a good response to antidepressant drugs [24], while other chronic pain patients share a more purely acute, nociceptive input and may therefore benefit from anti-Nerve Growth Factor (NGF) antibodies [25].

This concept of multimodal pain therapy, which encompasses advice and education, reassurance, exercise interventions, and manual and psychological interventions, combined with topical and oral drugs of different classes, has been fully incorporated in recent guidelines on chronic pain treatment [26,27]. Moreover, the available evidence also suggests the importance of interventional techniques such as epidural steroid injections to control radicular pain in the midterm and spinal cord stimulation to treat failed back surgery syndromes or complex regional pain syndromes [28,29]. More recently, a level of evidence of II with moderate strength of recommendation was found for lumbar radiofrequency ablation after diagnostic facet joint nerve blocks for chronic spinal pain [30].

These findings further confirm that several different strategies for pain control can be adopted at the same time, exploiting their synergistic action.

Opioids in Non-Cancer Pain: A Rational Approach

In the clinical armamentarium for the treatment of chronic non-oncological pain, therefore, opioids should be chosen only when the benefits on pain and function are expected to outweigh risk [31]. Even if low-quality at this time, very recent evidence supports the concept that long-term opioid therapy can be considered in some carefully selected and monitored patients, despite the dropout rate due to adverse events and deaths increasing with study duration [32].

However, pain therapists must know the intrinsic pharmacokinetic and pharmacodynamic properties, strengths, and limits of opioids, since these aspects can affect their analgesia and side effects profile. Weak opioids (codeine and tramadol) are generally recommended for mild-to-moderate pain, while strong opioids are suggested in patients who have not responded to weaker opioids [33]. However, in some cases, strong opioids at low doses are preferable for long term use given the reduced risk of dependency or abuse [34] and the

limited variability in plasma concentration compared to high doses of low-potency compounds, which further protects against the risk of overdose [35].

Moreover, opioids differ from each other in terms of Mu-Opioid Receptor (MOR) load, since morphine, fentanyl, and oxycodone show higher intrinsic activity on the MOR receptor. In contrast, others, the so-called "atypical opioids"or "multigesics" [36], have lower intrinsic MOR activity but show multiple mechanisms of analgesia. Tramadol, for example, combines relatively weak MOR agonist activity plus monoaminergic reuptake inhibition [37]. Buprenorphine binds with very high affinity at MOR and has lower affinity and intrinsic activity at delta and kappa-opioid receptors (DOR and KOR), plus Nociceptin/Orphanin (NOP) receptors [38]. Moreover, it acts as an antagonist at KOR and has shown a pharmacological profile of biased agonism in vitro, which may contribute to its antihyperalgesic effects [38]. The interesting and possibly protean agonistic profile of buprenorphine has recently been conceptualized [38].

Tapentadol was 'engineered' to combine MOR agonistic activity with inhibition of noradrenergic reuptake [39]. At the same time, cebranopadol has been called the first biased ligand, which is a ligand on MOR that preferentially activates the G-protein-linked effector pathway in preference to the β-arrestin pathway. Certainly, these different mechanisms of action could be linked with a potentially lower risk of respiratory depression and possibly other adverse effects, but clinical effectiveness needs to be confirmed in more extensive trials [40]. Finally, the chemical properties of the drug, the route of administration, the rate of administration, and the onset effect rate are key factors that also influence abuse potential and adverse events [41]. Molecules with low molecular weight and high lipophilicity cross the blood-brain barrier faster and have a rapid absorption rate. In contrast, drugs with high bioavailability following oral or intranasal administration will achieve higher plasma concentrations and are more likely to be abused. These features should all be kept in mind when prescribing an opioid for chronic non-cancer pain, together with other important features. The different pharmacokinetic profiles of opioid drugs can allow different choices to reduce adverse events in case of kidney or hepatic failure, or in the case of advanced age and dementia [42].

Therefore, the choice of the adequate drug, formulation, and dosage should always consider all of these aspects, starting with low doses and tapering carefully [43]. Moreover, a wise clinical approach should always consider deprescribing, i.e., reducing or discontinuing unnecessary or harmful medicines, even if, at the moment, the low level of evidence prevents drawing firm conclusions supporting the recommendation of any one particular opioid-analgesic-deprescribing strategy in patients with chronic pain [44].

Conclusion

The future challenge for pain treatment will be translating from a multidisciplinary approach to an interdisciplinary one [45] to better respond to patients' needs over time. An interdisciplinary team approach can assure a truly holistic strategy that accounts for the different pathogenesis of pain syndromes, their phenotypes, the nervous system involvement and remodeling, and the biopsychosocial components of chronic pain.

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Conflict of Interest

The authors have no conflicts of interest do declare.

Contributions

Conceived by CM, then all authors contributed equally to the manuscript.

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