



Not All Pain is Created Equal: Basic Definitions and Diagnostic Work-Up

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ABSTRACT

Chronic pain is considered a public health priority by the World Health Organization and European health institutions. It has reached alarming proportions in terms of disability, consumption of health and social resources, and impact on primary and specialist care services. Primary care physicians are often called on to manage this condition. Chronic pain management can be challenging due to its complexity. It has traditionally been considered to include nociceptive pain that persists longer than the normal healing time, neuropathic pain lasting more than 3 months, or a combination of these. More recently, a third descriptor, nociplastic (primary) pain, was added to classify patients with chronic pain

conditions such as fibromyalgia, nonspecific back pain, or mixed pain that persists or other conditions in which altered central pain modulation results in central sensitization and chronic pain in the absence of actual or threatened damage to tissues, including in the somatosensory nervous system. This document provides an overview of pain types and their underlying mechanisms. Successful pain management is facilitated by identification of the pain type. A set of diagnostic tools and a pain algorithm are presented to guide the clinician toward the correct diagnosis. The algorithm identifies cases that may require referral to a pain specialist. Once the site of origin of the pain (the “pain generator”) is identified, or a primary pain syndrome is suspected, the accompanying article provides information and rationale to support treatment decisions based on patient characteristics.

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Key Summary Points

Chronic pain is prevalent and burdensome.

This publication reviews the basic mechanisms underlying chronic pain and presents a pathway for identifying the points where painful impulses are generated or modified, the so-called “pain generators”.

We propose the SIMG 3.0 approach from the Italian Society of General Medicine to decrease misdiagnosis and promote the appropriate management of patients with chronic pain.

The accompanying article covers pharmacological treatment for patients with chronic non-cancer pain, based on the underlying pain generator and patient characteristics.

Patients with refractory chronic pain, especially pain with neuropathic or nociplastic characteristics, should be referred to specialty care.

institutions, and the Italian Ministry of Health. In a survey of prescribing practices and training needs for pain management among 636 Canadian GPs, development of skills for patient evaluation and differential diagnoses of chronic pain received the highest priority [3]. Pain education can improve the confidence and knowledge of GPs and outcomes for their patients with chronic pain [4–6].

Recently, the International Association for the Study of Pain (IASP) has updated its definition of pain as “*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*” [7]. Acute pain has a sudden onset, short duration, and is clearly associated with a cause. The IASP defines chronic pain as “pain that lasts or recurs for longer than 3 months [8]. Note that this inclusive definition establishes a pain duration but does not indicate a cause, thereby covering pain of uncertain origin.

Until recently, chronic pain conditions were not represented systematically in the International Classification of Diseases (ICD) maintained by the WHO. In the 11th revision of the ICD, a task force of the IASP has established a new classification of chronic pain that is applicable in primary care and specialized settings [9]. This classification distinguishes between chronic primary pain and six chronic secondary pain conditions (Box 1).

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13182746>.

INTRODUCTION

The clinical problem of “chronic pain” has reached alarming proportions in terms of disability, consumption of health and social resources, and impact on primary and specialist care services [1, 2]. This public health problem is considered a priority by the World Health Organization (WHO), European health

Box 1 Classification of chronic pain in version 11 of the International Classification of Diseases developed by the International Association for the Study of Pain and the World Health Organization [9]

Chronic primary pain [10]

Chronic secondary pain syndromes

- Cancer-related pain [11]
 - Postsurgical/post-traumatic pain [12]
 - Neuropathic pain [13]
 - Secondary headache/orofacial pain [14]
 - Secondary visceral pain [15]
 - Secondary musculoskeletal pain [16]
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Moderate-to-severe acute pain is a risk factor for developing chronic pain [17]. Most patients with chronic pain are managed in general practice [18].

Chronic pain can have a variety of mechanisms, and can include nociceptive, neuropathic, and or nociplastic (primary) pain. Rational choice of therapy is greatly facilitated by the correct diagnosis of the type and mechanism of pain, and identification of the points where painful impulses are generated or modified, the so-called “pain generators”. Comprehensive instruments are needed to accomplish this.

With reference to the IASP classification, we emphasize the difference between primary and secondary pain: the main role of a general practitioner is primarily to look after patients affected by secondary pain, since patients with primary pain are more complex and should be referred to multidisciplinary pain centers.

We propose the SIMG 3.0 approach from the Italian Society of General Medicine to decrease misdiagnosis and promote the appropriate treatment of chronic pain. The accompanying article provides an overview of pharmacological strategies based on the type of pain identified [19]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EPIDEMIOLOGY

Estimates of the prevalence of chronic pain among adults in the general population vary widely from 2 to 40% or more [20–22], although most studies report values between 10 and 30%. The variability may be due to how chronic pain is defined and how data is collected (e.g., telephone surveys vs. observational or registry studies) [23], or to social or cultural differences among populations [24]. In 1998, the WHO reported the results of a chronic pain survey conducted in 15 primary care centers around the world [25]. The overall estimated prevalence from 5438 random interviews was 22%, with wide variation between centers (range, 5.5–33.0%). A meta-analysis focusing on 28

low- and middle-income countries reported chronic pain in 34% of adults in the general population [26]. A pooled estimate of chronic pain among adult UK residents revealed a prevalence of 43.5% (95% CIs 38.4–48.6%) [27]. A survey of 6000 adults in Japan revealed a chronic pain prevalence of 39.3% [28]. The US CDC estimated the prevalence of chronic pain at 20.4% among adults, based on the 2016 National Health Interview Survey [29]. In France, a mail survey with nearly 25,000 respondents revealed a chronic pain prevalence of 31.7% [30].

PREVALENCE IN ITALY

An observational study published in 2005 involving 89 Italian general practitioners (1432 contacts) found that about one-third of outpatients in general medicine reported pain, and this was chronic in about half of cases [31]. In 2006, the Italian Society of General Medicine conducted a prospective study that identified 6155 patients who visited their GPs for pain not associated with infections or migraine. The estimated prevalence of chronic pain was 3% [32]. Results of a European study on pain in which 3849 phone calls and 300 in-depth interviews were conducted in Italy estimated the prevalence of chronic pain at 26%, with more women than men being affected [33]. This result was similar to that of a cross-sectional population survey of nearly 1300 adults in Narni, Italy, which revealed a chronic pain prevalence of 28.4% [34].

IMPACT OF CHRONIC PAIN ON QUALITY OF LIFE AND WORK PRODUCTIVITY

Chronic pain significantly affects physical and psychological health, impacting both function and quality of life [35–37]. It is often associated with anxiety or depression that may complicate management or exacerbate pain perception [38]. Chronic pain is responsible for increased use of healthcare resources [2, 39, 40] and loss of

work productivity due to absenteeism as well as reduced function [37, 41–44].

CRITICAL ISSUES REGARDING THE DIAGNOSIS AND TREATMENT OF CHRONIC PAIN IN GENERAL PRACTICE

1. GPs do not routinely explore the different components of pain in their assessment, citing a lack of time [45].
2. A structured and coherent approach to collecting the anamnesis and evaluating symptoms and signs to identify the type and origin of the pain is lacking [45].
3. The use of non-steroidal anti-inflammatory drugs in chronic pain therapy is excessive, and often inappropriate both in terms of efficacy and the risks of side effects [41, 46].
4. Opioid analgesic drugs are often not used when indicated in various care settings in Italy [48].
5. There is a lack of homogeneity in the use of specialist services, both in terms of which patients to refer and when to refer them [49].

DEVELOPMENT OF A DIAGNOSTIC ALGORITHM

Identification of these problems, combined with acknowledgement that chronic pain is a major problem and an increasing burden prompted the Italian Society of General Medicine (SIMG) to involve GPs, representatives of scientific societies, institutions, and patient associations in a consensus-building process and the elaboration of a document [50]. The output includes an algorithm for structuring diagnostic and therapeutic interventions for chronic pain in general medicine. The algorithm was refined during training courses organized by SIMG, which involved approximately 180 GPs, and was subsequently assessed and revised by a multidisciplinary work group initiated by the Italian Ministry of Health [51].

The resulting chronic pain algorithm for GPs consists of a structured evaluation with clinical tests that distinguish neuropathic from nociceptive pain and, thus, mechanical structural pain from pain linked to inflammation. The goal is to identify the site of origin of the pain (the “pain generator”) which, together with assessment of pain intensity, guides the most appropriate choice of therapy.

In pain literature [52], reference is made to the need to use various blocks in order to identify the origin of pain, by using two blocks with two different anesthetics (lidocaine and bupivacaine) for the duration of action, in order to reduce false positives and false negatives. It has to be said that this method replaces the use of placebo, which may raise significant ethical concerns. Two blocks with different anesthetics are considered by many clinicians (especially in the United States) to be an excessive cost for the healthcare system and, as we argue, should be used only in doubtful cases when the pain has not disappeared. Most clinicians believe that the use of lidocaine is indicative, for the duration of action of the local anesthetic, with the disappearance of both spontaneous and evoked pain. It should also be emphasized the pain relief obtained with the two different local anesthetics is perceived by the patient differently to the advantage of lidocaine. A successful result of the test is not only related to the anesthetic used but also to the active co-operation of the patient involved with it.

The algorithm identifies cases that may require referral to a pain specialist.

THE PROPOSED APPROACH

Differentiating among pain types can be difficult, but it facilitates identifying the correct therapy. A systematic approach is needed.

Basic Definitions and Implications

The Somatosensory System

Nociceptive neurons from sensory ganglia innervate somatic and visceral regions and connect to the spinal cord and brain stem, mediating sensory signal transmission from a

first neuron in the peripheral nervous system to a second neuron in the central nervous systems. The cell body of the first neuron is in the dorsal root ganglion of the spinal nerve (or sensory cranial nerve ganglia). The cell body of the second neuron is in the spinal cord (or brainstem) and decussates to the contralateral side in the spinal cord (or brainstem). These constitute the ascending pathway that initiates the awareness of pain. A second, descending pathway modulates pain perception by modifying conditions at the synapse between the first and second neurons of the ascending pathway. Spinal sensitization occurs when ascending impulses are amplified.

Pain Types

Nociceptive pain is the most common type. It plays a key role in sending warning signals to protect the body from (further) injury in response to noxious chemical, thermal, or mechanical stress. Pain receptors for these noxious stimuli have relatively high thresholds [54], compared for example to tactile receptors. Myelinated A-delta peripheral nerve fibers are involved in the rapid transmission of short-lived signal to the dorsal horn of the spinal cord, which then relays the signal to the central nervous system. Unmyelinated C peripheral nerve fibers transmit slow, long-lived impulses, for example nociceptive pain signals triggered by inflammatory mediators like histamine.

Box 2 Pain terminology from the International Association for the Study of Pain [53]

Nociceptive pain—Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.

Neuropathic pain—Pain caused by a lesion or disease of the somatosensory nervous system.

Nociplastic pain—Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.

Nociceptive pain can be further divided into somatic and visceral pain. Somatic pain is superficial or deep pain that originates in peripheral tissues (e.g., skin, muscle, bone). Visceral pain originates within the abdomen or specific organs (Box 2).

Neuropathic pain is a second general type of pain that arises “as a direct consequence of a lesion or disease affecting the somatosensory system”, [55]. Impulses are generated from ectopic sites due to damage or dysfunction of the peripheral nervous system (peripheral neuropathic pain) or central nervous system (central neuropathic pain) [55]. These ectopic impulses generate the sensation of pain in the innervated area (positive symptoms), while the nerve damage causes sensory deficits in the innervated area (negative symptoms). The location of these symptoms should be consistent with a neurological pattern. Depending on the cause, neuropathic pain can be generalized or localized [56]. The most relevant causes of peripheral neuropathic pain (PNP) include painful diabetic peripheral neuropathy (PDPN), postherpetic neuralgia (PHN), HIV-associated neuropathy (HIV-AN), and chemotherapy-induced peripheral neuropathy.

Neuropathic pain represents a significant burden for patients, society, and healthcare systems [57] that is associated with more severe pain, higher workplace absenteeism, and higher medical costs compared to chronic non-neuropathic pain [58]. It requires a different therapeutic approach from nociceptive pain and can be challenging to treat [59, 60].

A study conducted with 113 general practitioners in Italy who saw 58,480 adults over a 3-month period revealed a prevalence of chronic peripheral neuropathic pain of 0.77% [61]. Diabetic neuropathy and postherpetic pain were the two most common types (0.31 and 0.24%, respectively). Studies in the United Kingdom and France have estimated that among patients in the general population with chronic pain, 6–8% have neuropathic pain [30, 62]; whereas about half of the patients attending pain clinics have neuropathic pain. A systematic review of epidemiological studies of neuropathic pain in the general population revealed an estimated prevalence between 7 and

10% [63]. This is projected to increase due to population aging, rising obesity, and longer cancer survival with chemotherapy that may have neuropathic pain as a side effect [64].

A third pain type, called *nociplastic pain*, is defined by the IASP as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain” [53]. It can be considered a form of primary pain, which is defined as pain in one or more anatomical regions that (1) “persists or recurs for longer than 3 months”, (2) “is associated with significant emotional distress”, and (3) has symptoms that “are not better accounted for by another diagnosis” [10]. Whereas chronic secondary pain can be considered a symptom of another condition, in chronic primary pain, the pain itself may be considered a disease. Some of the conditions in this classification include chronic widespread pain such as fibromyalgia and complex regional pain syndromes, irritable bowel syndrome, and chronic nonspecific low back pain. These conditions often involve central sensitization [65] and may be associated with psychological distress, fear-avoidance, and pain catastrophizing. Patients may benefit from suitable cognitive and behavioral strategies.

The Central Sensitisation Inventory may be useful for identifying patients with key symptoms associated with this con [66]. It may be difficult to distinguish fibromyalgia from other conditions that cause chronic widespread pain [67]. In addition to quantifying the number of painful sites, an instrument like the FibroDetect[®] questionnaire for fibromyalgia can be useful for supporting diagnosis [68].

Differentiating Nociceptive and Neuropathic Pain

Screening tools (reviewed in [69]) include the Brief Pain Inventory (BPI) [70], the PainDETECT score [71], the LANSS [72] or the DN4 [73]. The LANSS and DN4 may be more specific because, in addition to the questionnaire, they include a rudimentary clinical assessment [74]. It is

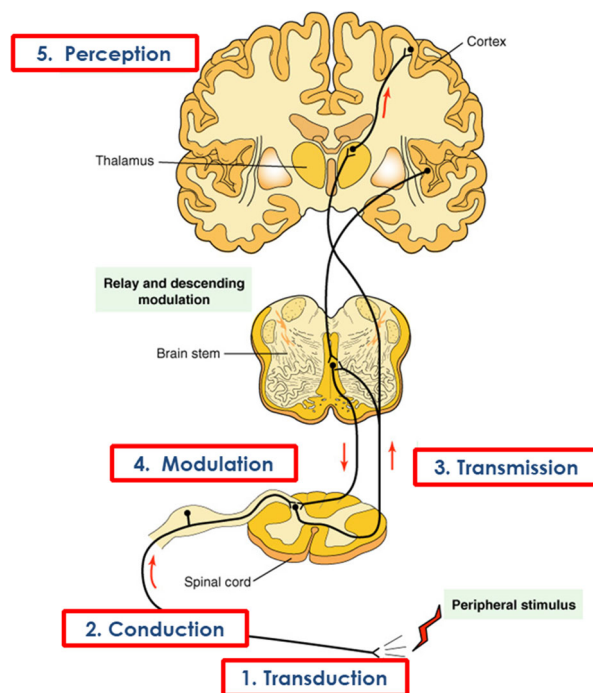


Fig. 1 Nerve impulse transduction, conduction, transmission, modulation, and perception. Modified with permission from Basic Neurochemistry. Molecular, Cellular and Medical Aspects. Edited by GJ Siegel, RW. Albers, ST Brady, DL Price. Chapter 57 Pain, M. Costigan et al. pp 927–937. VII Eds Elsevier [Copyright 2006. American Society for Neurochemistry]

important to note that while these tools are useful for screening purposes, they cannot replace a thorough clinical assessment [75]. A careful history, evaluation of the pain quality, and a neurological examination to assess sensory function can provide important clues to the type of pain. Careful delineation of the painful area and any sensory abnormalities permits identification of specific peripheral nerve or nerve root involvement (Fig. 1).

Mixed pain can occur in cancer patients when neoplastic growth causes damage to both somatic tissue and nerve tissue [76]. Although not clearly defined in guidelines (reviewed in [77]), mixed nociceptive–neuropathic pain can occur also in low back pain with radicular pain. In this case, inflammation from tissue damage causes and sustains the neuropathic pain [78]. Essentially, there is a partial nerve fiber lesion, such that ectopic discharges are stimulated by

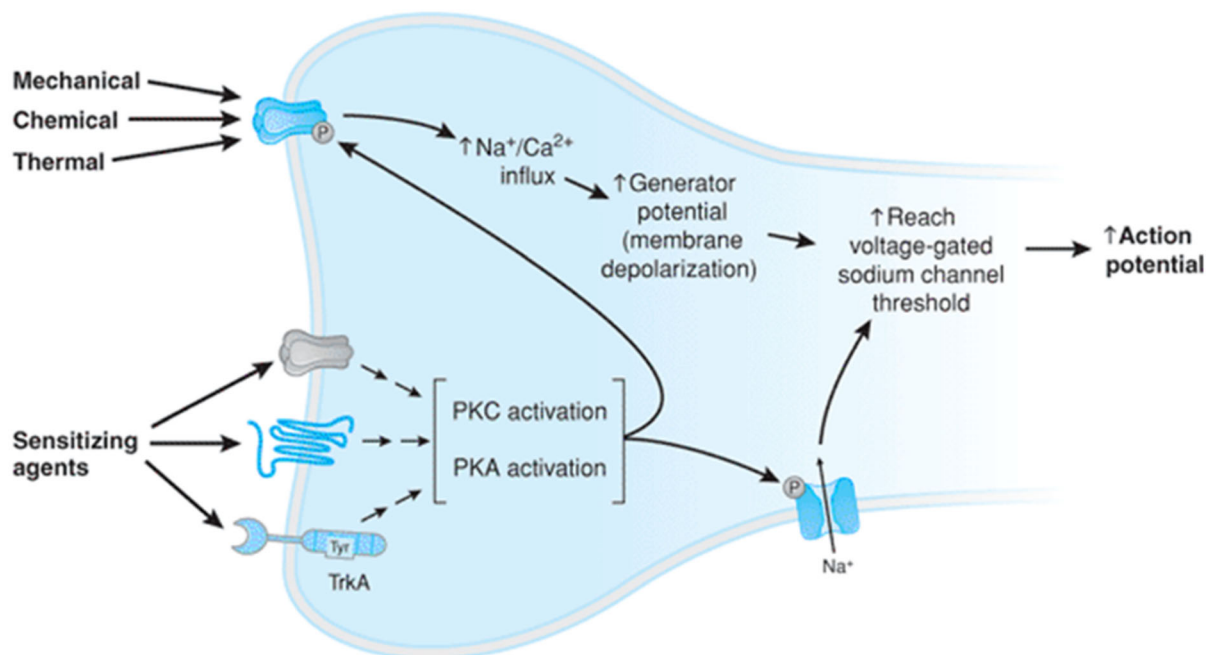


Fig. 2 Sensitizing agents lower the threshold for pain receptors. Reproduced with permission from Golan, David E., Armen H. Tashjian, and Ehrin J. Armstrong, eds.

mechanical or inflammatory stimuli, but the lesion is not severe enough to produce a conduction deficit. The resulting pain will be sensed in areas compatible with innervation. Chronic lower back pain may also be primary musculoskeletal pain, especially if accompanied by significant psychosocial contributors.

Activation of pain signaling in response to a painful stimulus is not static. The pain threshold, or sensitivity, can be modulated by a large variety of sensitizing agents (e.g., prostaglandins, inflammatory cytokines, etc.) (Fig. 2).

Hyperalgesia occurs when nociceptors detect a noxious stimulus as more painful than expected. Allodynia occurs when a completely non-noxious stimulus (e.g., light touch) causes pain. Allodynia can also result from damaged nociceptors on peripheral nerves. Hyperalgesia and allodynia may be associated with either nociceptive or neuropathic pain, although the underlying mechanisms are different. In the case of nociceptive pain, allodynia is mainly the result of peripheral sensitization and is often called primary allodynia to underscore the fact that it identifies the pain generator. Sometimes the area of allodynia extends beyond the pain

Principles of pharmacology: the pathophysiologic basis of drug therapy. Lippincott Williams & Wilkins, 2011

generator. This phenomenon is due to central sensitization that causes an enlargement of the receptor fields in the spinal cord and is called secondary allodynia.

In neuropathic pain, allodynia, which is often called mechanical or dynamic allodynia, is due to more complex mechanisms that involve modification of the electrical activity at the ectopic site on damaged fibers, combined with central sensitization. In central sensitization due to peripheral neuropathic pain, there is extensive participation of wide dynamic range (WDR) neurons that connect tactile fiber activity with the nociceptive pathways.

Referred pain is perceived in a location other than where it originates. Figure 3 schematically illustrates the possible patterns of referred pain (consult anatomical maps for more detailed information). The pain is always referred to a site outside the territory of innervation of the responsible structure, but generally in the same spinal segment (convergence; e.g., the arm in angina, the shoulder in biliary colic) or when two organs share overlapping peripheral innervation (dichotomy; e.g., colon and bladder).

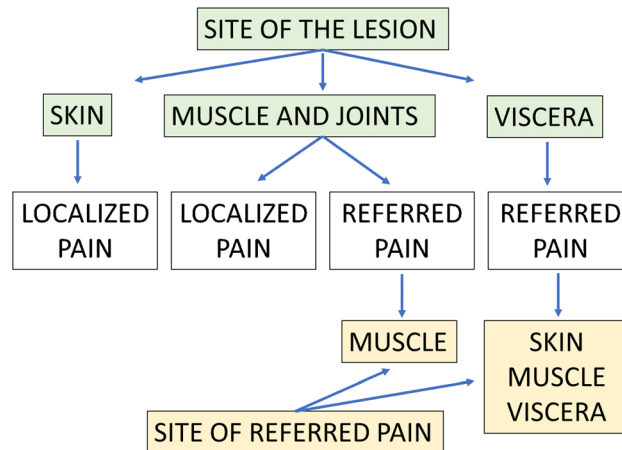


Fig. 3 Referred pain patterns

Visceral pain may be referred to specific superficial sites.

Referred pain should not be confused with secondary allodynia, in which spinal sensitization enlarges the area where pain is perceived and where pain can be elicited with normally painless stimuli.

DIAGNOSTIC WORKUP USING THE SIMG METHOD VERSION 3.0

The diagnosis is made by combining the information reviewed in the previous sections with

the results from the six observations/tests below, which can be performed in the office using the simple tools shown in Fig. 4.

Diagnostic Workup

From the patient's medical history, determine whether they have a neurological condition that is associated with nerve fiber lesions, such as multiple sclerosis or herpes zoster infection.

1. The first step is to delineate the affected *area* with a whiteboard marking pen to outline the confines of the *area* in which pain or

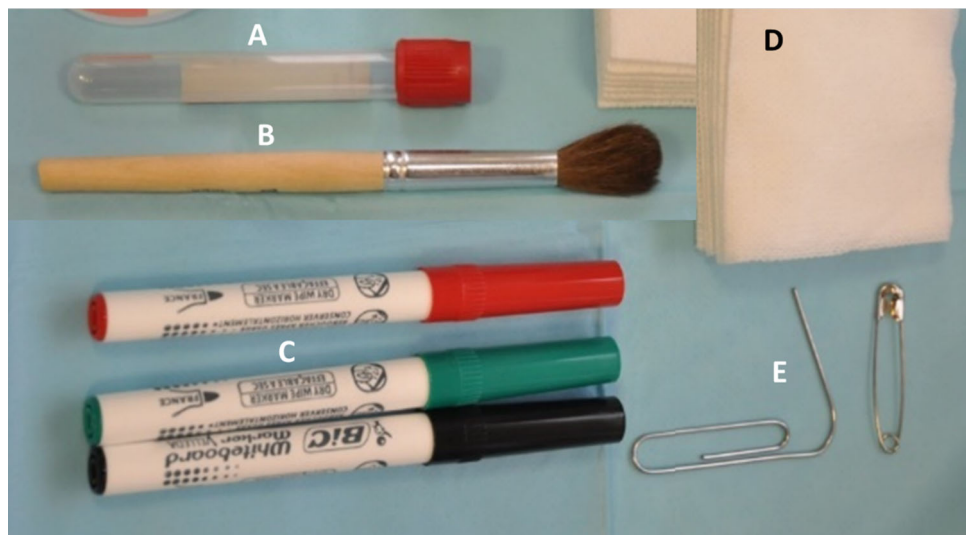


Fig. 4 Simple instruments for conducting the pain assessment. **a** A tube of warm water (40 °C), **b** a soft-bristle brush, **c** whiteboard markers in 3 colors, **d** soft cotton or gauze, **e** sharp objects such as a paperclip or pin



Fig. 5 Topographic definition of the symptomatic area

discomfort is provoked by light touch. Once this area is circumscribed, we use the red pen to identify the zone(s) of major pain within this area (Fig. 5).

2. Are there particular elements in the painful area (e.g., corresponding to a plexus, root or nerve)?
3. *Are there any signs of somatosensory system deficiency?*

Three stimuli are used to test for sensitivity to light touch discrimination (cotton ball or gauze), pinprick (paperclip/pin) and temperature (tube of water at 40 °C) (Fig. 6).

Explain the procedure to the patient, including the purpose of the assessment: “I will now test the sensibility inside the area and compare it to outside of the area. When I ask whether you feel the stimulus, please respond yes or no”. Touch lightly with the cotton ball inside the area and compare to outside (contralateral location), asking for a

response at each touch. Repeat this procedure with a gentle poke using an opened paperclip and then again with the tube of warm water. From this assessment, we can determine whether the patient has partial or total sensory deficits indicative of neuropathic pain (Fig. 6). Assessment of sensation within the affected area and comparison with surrounding unaffected area.

4. *Are there any signs of receptor sensitization (primary allodynia)?*
5. *Are there any signs of spinal sensitization (secondary allodynia)?*

This is tested by applying gentle strokes with a soft bristle brush in and adjacent to the pain area. If secondary allodynia is

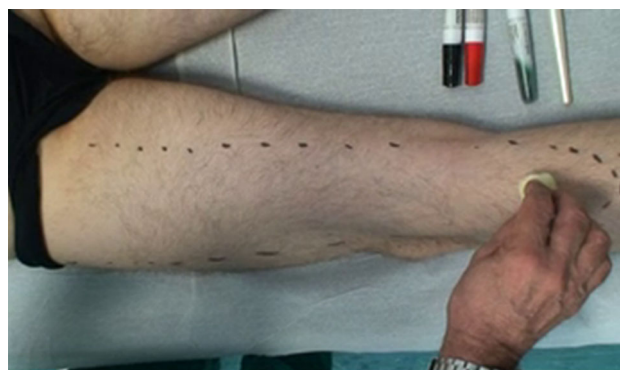


Fig. 6 Assessment with a cotton swab of tactile sensitivity in the pain area declared by the patient

B

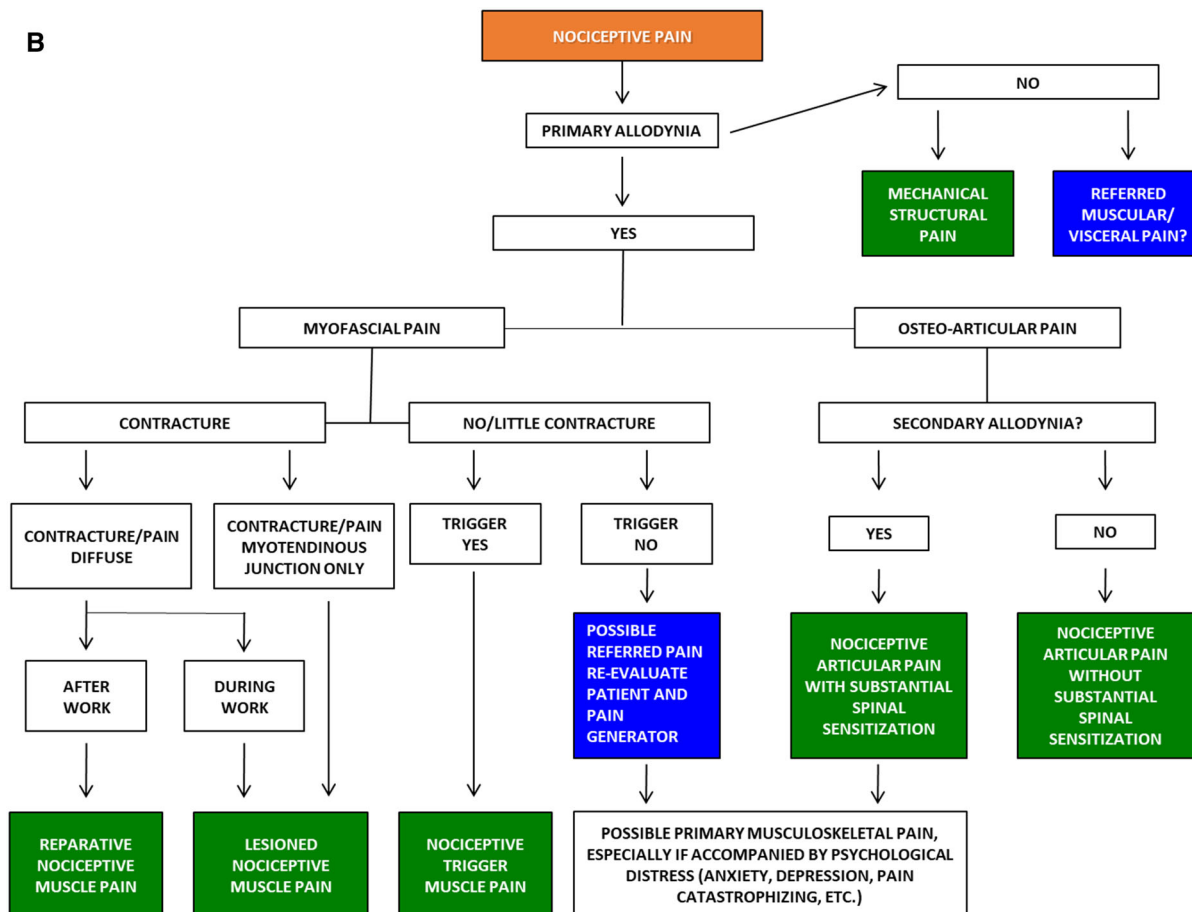


Fig. 7 continued

A clinical assessment revealed signs of tactile sensitivity deficit and stinging in the area in which the patient felt tingling (that is in the dermatome of the 5th lumbar root). A further MRI check revealed an intraforaminal disc herniation (right-sided). A sensitivity assessment can prove to be essential, while pain distribution is only indicative. It is always necessary to consider that for each spinal root there is a dermatome in which superficial sensitivities should be evaluated and a different territory of deep pain.

CONCLUSIONS

This algorithm, developed by the Italian Society of General Medicine (SIMG), is currently offered as a part of Continuing Medical Education for GPs in Italy. The goal is to provide primary care

physicians with the diagnostic skills needed to manage patients presenting in general practice with chronic pain or refer them to specialty care when appropriate. The accompanying article in this issue provides information and rationale to support treatment decisions based on type of pain and patient characteristics identified here.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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