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Osteoarticular pain: therapeutic approach by paradigms

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Abstract. – Osteoarticular pain is a common condition in the adult population. It is a nociceptive pain modulated by different factors, and it is one of the major symptoms that force patients to seek medical advice. Since osteoarticular pain has a complex pathophysiology and it is not a linear condition, we propose in this paper an original approach to osteoarticular pain by paradigms, where a paradigm refers to a framework of concepts, results, and procedures within which subsequent work is structured. The paradigm presented is a conceptual tool that could help clinicians to choose the correct therapy considering both pain characteristics and clinical features.

Key Words:
Rheumatology, Traumatic pain, Rehabilitation, Post-surgery pain, Opioids, NSAIDs, Paracetamol.

Introduction

Pain has been recently re-defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[1].

In its acute nociceptive manifestation, it is essentially a physiological phenomenon aimed to warning individuals about their exposure, or even the possible exposure, to high-intensity energies that can cause injuries to them, such as mechanical energy (the impact with a moving body), thermal energy (too high or too low temperature) or chemical energy (low or high pH)[2].

Conventionally, pathological pain has been identified with chronic pain, i.e., "a pain that persists past normal healing time and hence lacks of the acute warning functional component of physiological nociception"[3]. Indeed, the recent IASP classification distinguishes between chronic secondary pain, in which a previous injury is generally recognizable, and chronic primary pain, which is caused by the malfunctioning of the nociceptive system. Although the operative definition of chronic pain is based on a purely temporal criterion, all different types of chronic pain share a common feature: the violation of one or more rules proper of physiological nociception[3]. Pain is one of the major symptoms for which the patient is forced to seek medical advice.

Pain in diseases of the musculoskeletal system is a vast and complex topic, in its nosographic definition, in the pathogenetic mechanisms, in the therapeutic choices, and in the epidemiological dimension of the problem, since over one-fifth (22%) of the European population has, or has experienced, long-term muscle, bone and joint problems, such as rheumatisms and arthritis[4]. Its complexity is explained by the various pathogenetic mechanisms, in the many topographical locations and the wide variety of tissues, which are sources of pain.

To analyze osteo-articular-muscular pain, it is necessary to split this large chapter into four main areas, identifying the trauma patient, the post-surgical patient, and the patient with an orthopedic-rheumatologic condition, under medical treatment, not yet surgical. The orthopedic-rheu-

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matologic oncology patient will gravitate into the oncology orbit. The three domains should then be related first to the biological age of the patient, and then to his/her specific clinical profile.

Pain is the major symptom that often defines the pathognomonic diagnosis and directs towards the differential diagnosis and clinical-instrumental to therapy. Its description is very important but often vague. Wylde et al[5] in 2011 got 15 different definitions of persistent pain after knee or hip prosthesis from 1,300 patients. The correct definition of pain in the context of the specific clinical problem is then the premise for the most appropriate, viable choice of pharmacological and nonpharmacological therapy.

The approach to therapy requires a general methodological definition, in which the individual patient during the specialist consultation about his poly pathological and poly pharmacological profile can be contextualized. In this paper, we propose an original approach to the pain of the locomotor apparatus by paradigms. It is a conceptual tool that contributes to give a unitary form to data or clinical results, both known and still open to new solutions.

Physiopathology of Osteoarticular Pain

To better interpretate patients' pain, the distinction between different types of pain and their physiopathology is mandatory. Although the operative definition of chronic pain is based on a purely temporal criterion, all different types of chronic pain share a common feature: the violation of one or more rules proper of physiological nociception[3]. Although there are hundreds of pathologies characterized by the presence of pain, the pathogenetic mechanisms of pain, in their essential aspects, are very few. In terms of pathogenetic mechanisms, we recognize inflammatory and mechanical pain, which both belong to nociceptive pain, neuropathic pain, mixed pain (that is pathogenic mechanisms that can be traced back to both inflammatory and neuropathic pain), and nociplastic pain (for example fibromyalgia), in which nor inflammation, nor neuronal damages could be demonstrated, and pain is probably sustained by central sensitization mechanisms.

Inflammatory Pain

Peripheral terminals of somatic and visceral afferent nociceptive fibers are high-threshold neurons, specialized in responding to highly intense stimuli. During inflammation, peripheral terminals lower their activation threshold and increase their excitability, a phenomenon known as peripheral sensitization. Peripheral sensitization relies on molecular modifications of receptors and channels, normally involved in nociception, due to several mediators released by immune cells in the inflamed tissues. Peripheral sensitization is the main violation of inflammatory pain and implies that physiological conditions, such as the normal body temperature, are enough to sustain pain from inflamed tissue (spontaneous pain) or innocuous stimuli, such as a gentle touch or pressure on the inflamed site, evoke pain (allodynia) or drastically increase a pre-existing pain (hyperalgesia). The "inflammatory soup", responsible for peripheral sensitization, contains different molecules, including protons, free radicals, ATP, but the most prominent effects are due to prostaglandins and cytokines[4]. In both acute and chronic inflammatory pain, spinal cord is early involved in pain modulation and generation, for instance by lowering the spinal threshold. The role of spinal sensitization in the different types of pain will be discussed below.

Since peripheral sensitization is the hallmark of inflammatory pain, drugs acting on peripheral sensitization inhibit prostanoids and cytokines synthesis, which are the main responsible for this phenomenon. Traditional NSAIDs, COXIBs and corticosteroids belong to this group. NSAIDs and COXIB inhibit COX-1 and COX-2 with different selectivity and potency. They are appropriate in all forms of inflammatory pain, but their efficacy is limited in chronic inflammatory pain, and they should be combined with other drugs. The anti-inflammatory activity of corticosteroids mainly depends on the inhibition of the transcription factor NFκB, which regulates the expression of several pro-inflammatory cytokines, including IL-1, IL-6, TNFα, INF-γ, some enzymes, including COX-2 and inducible NOS, and proteins variously involved in inflammation. Corticosteroids are often used for their anti-edema properties in neuropathic pain, thus reducing the compression on nerve fibers.

Mechanical Pain

Mechanical pain is a type of nociceptive pain that often affects joints, in particular knees and hips, even in the absence of inflammation. It is caused by the destruction of the articular cartilage and the "exposure" of the subchondral bone,

which is widely innervated by nociceptive fibers. The contemporary decrease of the synovial fluid makes subchondral nociceptive fibers unprotected from mechanical stimulation due to body's weight. This type of pain is not due to peripheral sensitization, as the inflammatory pain, and this is the reason why it poorly responds to NSAIDs.

Neuropathic Pain

Neuropathic pain is the consequence of a lesion or disease of the somatosensory system and can be classified according to the site of injury, peripheral or central, and type of pathology, etiologically distinct. The etiology could be metabolic (diabetic neuropathy), traumatic (nerve injury), vascular (stroke), neoplastic (tumor compression), infectious (post-herpetic neuralgia, borreliosis), toxic (chemotherapy neuropathy), immunological (multiple sclerosis), genetic (Fabry neuropathy) or unknown, as in the case of idiopathic neuropathies. Neuropathic pain is often paradoxically accompanied by loss of function and can continuously persist or manifest with recurrent painful episodes, in which it can be spontaneous or evoked.

Although each type of neuropathic pain has its own peculiarities, common violations of physiological nociceptive pain can be recognized. First of all, pain does not arise from tissues, such as in nociceptive pain, but from an ectopic site inside the somatosensory system, with a variable extension along the fiber. The main feature of the ectopic site is the exacerbated electrical activity determined by an altered expression of channels, with a decrease in potassium channels, that contribute to stabilize the plasma membrane, and the presence of specific types of hyperactive voltage-gated sodium channels, normally present only in the embryonic life. Thus, the ectopic site is responsible for the generation of high-frequency action potentials that are centripetally conducted towards the next synapse, causing the release of huge amounts of neurotransmitters. At the synapse, such as the spinal synapse in the case of peripheral neuropathic pain, it has been demonstrated a second violation of normal nociception: the overexpression, up to 10 times, in the number of N-type calcium channels, which are normally responsible for calcium entry and glutamate release. This implies a huge glutamate release, also supported by the high discharge rate of the peripheral fiber, and a pathological transmission of stimuli[6]. Therefore, in neuropathic pain, blocking the activity of voltage-dependent sodium channels and blocking N-type calcium channels are first-line pharmacological strategies.

These drugs act directly on the damaged nerve fiber and include voltage-gated sodium channel blockers and alfa$_2$delta ligands. Voltage-gated sodium channel blockers arise as anticonvulsants, antiarrhythmics, or as local anesthetics and include carbamazepine, oxcarbazepine, lamotrigine, and lidocaine. They counteract the generation of ectopic discharge and the propagation of action potentials along the damaged fibers. Alfa$_2$delta ligands act on N-type calcium channels and include pregabalin and gabapentin. Despite the name, their mechanism of action does not involve the GABAergic system. As previously described, in peripheral neuropathic pain there is also a modification affecting the pre-synaptic membrane of the proximal fiber entering the spinal cord, with an increase up to 10 times in the expression of the N-type calcium channels. This phenomenon is believed to be due to an accumulation of the channel in the cell membrane which is removed by binding of gabapentinoids to the accessory alfa$_2$delta subunits that control channel trafficking[6]. Both voltage-gated sodium channel blockers and gabapentinoids are appropriate for neuropathic and mixed pain.

Nociplastic Pain

The term nociplastic pain has been recently coined to describe a type of pain in which neither inflammation nor lesion of neurons can be appreciated, and pain relies on malfunctioning of the nociceptive system. Indeed, the term 'nociplastic pain' takes the place of the term 'dysfunctional pain', with the purpose of stressing on the notion that maladaptive neuroplasticity has a pivotal role in this type of pain. Maladaptive neuroplasticity can be defined as a functional and structural reorganization of nociceptive pathways, which lose the ability of modulating nociceptive stimuli and even become responsible for their generation. This phenomenon is also known as central sensitization. According to the last IASP classification, the category of chronic primary pain includes several different pathologies which are sustained by nociplastic mechanisms, such as fibromyalgia.

Spinal Sensitization

In chronic peripheral pain based on inflammatory, neuropathic or mixed mechanisms there is always a massive release of glutamate and other relevant neurotransmitters, such as ATP, in the spinal synapse with a greater postsynaptic depolarization. This persistent depolarization removes

the Mg^{2+} voltage-dependent blockade of NMDA receptors, the other class of glutamate receptors expressed in second-order neurons, which are extremely permeable to calcium ions. The activation of the NMDA receptor is an essential step in spinal sensitization, a phenomenon that always accompanies chronic pain, in which the spino-thalamic neuron lowers its activation threshold and transmits nociceptive stimuli more easily. In fact, calcium participates in phenomena of pathological remodeling of the synapse and spino-thalamic neuron, acting as a second messenger and activating kinases. In chronic secondary pain, the spinal synapse represents a paramount pharmacological target, in order to reduce nociceptive transmission and limit the phenomenon of synaptic plasticity that worsens the painful state and sometimes can evolve into nociplastic pain[7].

Different drugs interfere with spinal synaptic transmission and through this action counteract the establishment and effects of sensitization[8]. Paracetamol is classified among NSAIDs, with which it shares the antipyretic and analgesic actions, but it does not possess anti-inflammatory activity. Its belonging to this pharmacological class depends on its ability to inhibit COX-1 and COX-2 *in vitro*. However, its power of inhibition is very low compared to other members of the class. Furthermore, the action of paracetamol is inhibited in situations of high concentration of peroxides, as typically happens in inflamed tissues. Part of analgesic effects of paracetamol depends on the production of a metabolite in the CNS, known as AM404, which is very similar to anandamide, one of the most important endogenous cannabinoids. Therefore, paracetamol, through its metabolite, would enhance the endocannabinoid tone in numerous areas of the nervous system, including the dorsal ganglia and the dorsal horns of the spinal cord, where the metabolite performs part of its analgesic activity[9]. Opioid drugs, such as morphine, oxycodone, hydromorphone promote analgesia by acting on μ type opioid receptors in the brain, in the brainstem, and, especially, in the spinal cord, thus activating the main endogenous analgesic system. Opioids produce analgesia by multiple actions. However, the coupling of opioid receptors to ion channels for potassium and calcium is believed to be the most important mechanism by which both endogenous and exogenous opioids produce analgesia. At the spinal level, presynaptic μ receptors inhibit the opening of N-type calcium channels, preventing the entry of calcium and the vesicular release of neurotransmitters. On the post-synaptic neuron, the μ receptors cause the opening of potassium channels and the outflow of these ions thus determining hyperpolarization and reduced excitability of the spino-thalamic neuron. Figuratively, opioids render the nociceptor "mute" and the spino-thalamic neuron "deaf", achieving a profound inhibition of the spinal synapse that underlies their powerful analgesic activity[10].

Descending Inhibitory Mechanisms

The brainstem plays a crucial role in the modulation of pain processing at the spinal cord level. Fibers originating from the periaqueductal grey (PAG) and *Locus Coeruleus* release serotonin norepinephrine, a dopamine that directly or by recruiting interneurons (for instance opioid interneurons) inhibits the transmission at the spinal synapse. However, also facilitatory stimuli can arise from brainstem and an imbalance between facilitatory and inhibitory mechanisms has been implicated in the development of chronic pain states.

Pharmacological manipulation of the descending pathways can be obtained according to three different strategies: increasing the discharge of the descending pathways, prolonging the action of serotonin and noradrenaline at the spinal synapse or mimicking their action. There are several drugs that possess the property of activating the descending pathways. For instance, both opioids and gabapentinoids, by acting in the brainstem, can inhibit inhibitory interneurons whose activity prevents the discharge of descending pathways: an inhibition of an inhibition. The second strategy is the best known: the use of serotonin and norepinephrine reuptake inhibitors: tricyclic antidepressants, such as amitriptyline, or SNRIs, such as duloxetine and venlafaxine. The third strategy mainly concerns agonist drugs directly stimulating α2-adrenergic receptors expressed in the spinal cord: clonidine and dexmedetomidine.

Chronic pain infrequently responds to a unique drug and combination therapy is often required. A better understanding of the mechanisms of action of drugs in the context of the pathogenetic processes with which they interfere will help to maximize therapeutic benefits, minimizing adverse effects.

Methodological Approach by Paradigms

For the management of osteoarticular pain, the approach for therapy treatment normally comes

from the consultation of the guidelines and good practice statements that Scientific Societies elaborate and provide within each medical scientific area. All guidelines usually contain information from an up-to-date systematic study of a problem to make a diagnostic or therapeutic appropriate decision. The specialists are provided with the most up-to-date data from the literature to prepare an appropriate clinical reasoning.

The final clinical decision could also derive from an algorithm, as a sequence of elementary operations which leads to a final result in order to solve a specific class of problems. A peculiar feature of the algorithm is that the operations must be elementary, unique, non-redundant, and in a limited number. For the pharmacological treatment of osteoarticular pain, the algorithm may be useful with reference only to the characteristics of the disease-pain relationship, since the decision cascade puts the various drugs in a time sequence, considering the therapeutic outcomes of each pharmacological class, and often not to safely patient in a peculiar clinical condition.

In consideration of clinical conditions, the input data in the algorithm could be numerous, the interpretation could become ambiguous, and the number of steps could increase. This approach disregards the evaluation of the patient in its uniqueness and complexity, which includes the whole osteoarticular disease and not only the pain symptoms.

In the current work, a multidisciplinary group composed by pain therapists, orthopedics, physiatrists, rheumatologists, and pharmacologists have chosen the paradigm as the analysis criterion, defined also as the disciplinary matrix of a scientific community regarding a specific problem. It defines, analyzes, and deepens the research topic, identifying the object of the analysis, the most important problems, and the most appropriate technique to address them, aiming to reach the more appropriate therapy for each patient.

The canonical approach recommended by international guidelines impose a choice of drugs referring to pain intensity, in a chronological order which starts with paracetamol or FANS or COXIBs and then passes to opioids if the first ones are ineffective. In the paradigm approach we add the global vision of the patient to these notions and his pathology, also considering any pain type. This paradigmatic vision puts the three categories of analgesics at the same level, because the choice will be driven by the specific conditions of the patient. For these reasons, the paradigm could be considered as the most appropriate pathway for the best understanding of the pain symptom that cannot be schematized into all its components, since: it involves anatomical districts with different morphologies, topographical anatomies, and algogenic sources. Pain could originate from these districts because of traumatic events, sometimes very different from each other; it originates from surgical interventions of different complexities and in very different districts (arthroscopy/vertebral stabilization), it accompanies all orthopedic diseases not yet surgical and rheumatological diseases, and it could be present in different degrees during the rehabilitation process.

Following these concepts, we identify four types of paradigms: traumatic, orthopedic, rheumatologic and post-surgical pain.

For the schematization of the traumatic, orthopedic and rheumatologic paradigms' pain, the main items to drive the correct therapy are identified. First of all, we have to distinguish acute pain and chronic pain, persisting over three months, characterized by a non-protective function and a lack of balance between amplification and inhibition, but it is considered to be as a painful disease state.

Then, the next distinction to be done, proper of the general definition of pain, is between: nociceptive (mechanical and inflammatory) with a protective role, due to the activation of neurons at the high threshold by nociceptive stimuli, thermal, chemical, myotendinous stretch; neuropathic, that originates from the alteration of nociceptive signals by amplification of noxious stimuli with pain, even in the absence of the stimuli themselves (radiculopathy); inflammatory, due to hypersensitivity of nociceptors, due to inflammation of peripheral tissues and sensitization of the nociceptive system, spinal pain from spondylodiscitis, joint pain from rheumatic disease; nociplastic**,** due to the amplification of nociceptive signals in the absence of nerve injury or inflammation, fibromyalgia, chronic widespread pain. In each general definition of pain, the following descriptors will be described: onset (sudden, slow, worsening); characteristics (cramp-like, uretic, pressing, constrictive, piercing, dull, etc.); course (intermittent, remitting, continuous); site (diffuse, circumscribed, radiated, variable); correlations (psychological, social, quality of life impact); spontaneous or evoked. Indicators of intensity, such as VAS (Visual Analogue Scale), NRS (Numerical Rating Scale) or WOMAC (Western On-

tario and McMaster Universities Osteoarthritis Index) should be added[11,12].

The analysis of pain symptoms is then correlated to the individual patient, which cannot be included in the general paradigm, but contextualized by each specialist considering the patient's comorbidities and polytherapy, resulting in a better therapeutic offer.

Traumatic, orthopedic and rheumatologic paradigms are briefly analyzed in relation to their peculiar nosology. For each paradigm, case reports from clinical practice with the characteristics of pain, comorbidities and polytherapy of patients reported are proposed in Table I, II and III.

Post-surgery pain is characterized by a major uniformity of the clinical profile for origin, pathogenesis and intensity, so that it may not be divided in different types of pain. Because of the prevalence of the severe intensity of pain, the analgesic choice will be mainly addressed to opioids, associated to specialist interventional techniques. For the following days, the management of pain after immediate post-surgery follows the specific paradigm of the original pathology.

From the identification of the pain of a specific pathology, its intensity, the state of the patient, such as comorbidity and drugs used for these conditions, we arrive to a rational suggestion for analgesia.

To consider the paradigm's methodology effective and to achieve an optimal pain treatment, some general contraindications can never be ignored or underestimated in the assessment of patient clinical conditions: (a) heart disease and chronic renal failure need a prudent administration of anti-inflammatories, whether NSAIDs or COXIBs; (b) treatments with NSAIDs must also consider the possible side effects on the gastro-enteric system, thus they have to be used with great caution in case of ulcerative diseases or inflammatory bowel diseases, however favoring the co-administration of gastroprotectors; (c) diabetes mellitus induces the sparing use of steroids, seriously controlling glycemic levels, also considering the possible drop in values where the increased blood sugar has been further aggravated by the arthritic disease not yet treated; (d) anticoagulant drugs, especially warfarin and acenocoumarol, but also the most modern NAO, requires careful surveillance of the hemorrhagic risk (or, on the contrary, of the thrombotic risk), secondary to the simultaneous administration of NSAIDs or COXIBs, as of other various drugs, especially if used intra-articular infiltratively where the risk of hemarthrosis must always be considered; (e) the prolonged use of steroids must also assess the risk of secondary osteoporosis, hypertension and glaucoma.

Pain in Traumatology

Pain is the main, predominant symptom of a traumatic event, and depends on the specific gravity of the harmful event. Traumatic pain is nociceptive, acute to different degrees, evoked by high intensity stimuli, well localized, and somatic; it is characterized by a precise stimulus-response relationship. In trauma, acute pain induces defense reactions that tend to compensate or remove the cause of the pain itself, often activating some neurovegetative functions (e.g., increased respiratory activity and blood pressure, tachycardia). On the other hand, chronic pain is the painful sensation persisting for at least 3 months after the phase of acute pain beyond the normal healing time: in this case the pain has no biological utility and then turns into pain-disease (e.g., pseudoarthrosis). To manage post-traumatic pain, a clinician should act centrally and peripherally, in synergistic correlation (Table I). Nociceptors are responsible for post-traumatic pain. Of the two main categories of nociceptors, Ad-type nociceptors are the ones involved in trauma, activated by mechanical, as well as thermal stimuli of high intensity and are responsible for the transmission of the first pain sensation (acute, pungent, well localized, and short). A severe trauma that is accompanied by an increased release of noradrenaline can cause a sort of amplified reactivity towards subsequent stimuli and an excessive consolidation of traumatic memories. A contusive trauma on the integument and/or underlying structures of any part of the body, is correlated to the extent of the injury event and the neuroendocrine response.

In a distortion trauma or, in cases of a greater injury, a dislocating trauma, the traumatic target is represented by the capsular-ligamentous structures. The paradigm of pain becomes more peculiar, due to the affected joint and its morphofunctional complexity, the degree of injury of the structures (elongation, partial injury or frank rupture), and the concomitant involvement of neighboring structures. In fractures, the source of pain is represented by nociceptors present in the bone and in the periosteum, and by stimulation of capsular-ligamentous nociceptors in articular fractures. However, it appears that the periosteum

Table I. The methodological Paradigm of traumatological pain in some exemplary specific situations (cases report) to make the appropriate choice of the analgesic drug. The specialist bases the choice on a decision-making paradigm for the individual patient.

	Traumatic pain paradigm				
	Type of pain	**Acute**			
	Definition	**Nociceptive-mechanical**	**Nociceptive-inflammatory**	**Neuropathic**	**Mixed inflammatory/neuropathic**
Intrinsic factors pain	Descriptor Cause of pathology/ pain	Localized, at load, at decubitus, at palpation Hip contusion	Mechanical, nocturnal, flogosis ++ Post-traumatic arthritis	Irradiated, paresthesias Elbow contusion, (posterior interosseous nerve)	Sudden, irradiated, paresthesias Cervical whiplash
Conditions to consider	Comorbidity Therapies in place Intensity of pain	Pacemaker TAO Depending on NRS (NRS ≥ 7 strong opioids)	Hypertension, Diabetes Antihypertensives, antidiabetics Depending on NRS (NRS ≥ 7 strong opioids)	Headache Pregabalin Depending on NRS (NRS ≥ 7 strong opioids)	Heart disease, hypertension, atrial fibrillation, hypercholesterolemia Antihypertensives, antiarrhythmics, NOA, statins Depending on NRS (NRS ≥ 7 strong opioids)
Indications/ suggestions therapeutic class	Related therapy options	Paracetamol and/or opioids short acting (NSAIDs are contraindicated)	Paracetamol + opioids short acting, Antiedema; Caution with NSAIDs	Short-acting or strong opioids Paracetamol, Steroid	Paracetamol + weak or strong opioids, long-acting opioids, myorilaxants, adjuvants, steroids

Abbreviations: NSAIDs, Non-steroidal anti-inflammatory drugs; NOA, New oral anticoagulants drugs; TAO, Oral anticoagulant therapies; NRS, Numerical rating scale.

Table II. The methodological Paradigm of orthopaedic pain in some exemplary specific situations (cases report) to make the appropriate choice of the analgesic drug. The specialist bases the choice on a decision-making paradigm for the individual patient.

		Orthopedic pain paradigm			
	Type of pain	Chronic			
	Definition	Nociceptive-mechanical	Nociceptive-inflammatory	Neuropathic	Mixed inflammatory/neuropathic
Intrinsic pain factors	Descriptor Cause of pathology pain	Continuous Gonarthrosis	Occasional, localized, load Gonarthrosi (with bone edema)	Sudden, irradiated, paresthesias, at rest Operated disc herniation	Always orthostatic/sitting Lumbar stenosis
Conditions to consider	Comorbidity Therapies in place Pain intensity assessment	Hypertension Antipertensives, Depending on NRS (if NRS ≥ 7 strong opioids)	Hypertension Antipertensives, ASA Depending on NRS (if NRS ≥ 7 strong opioids)	Irritable colon, gastropathy, anxiety Anxiolytics, gastroprotectors Depending on NRS (if NRS ≥ 7 strong opioids)	Heart disease, hypertension, atrial f, hypercholesterolemia Antihypertensives, antiarrhythmics, NOA, statins Depending on NRS (if NRS ≥ 7 strong opioids)
Indications/ suggestions therapeutic class	Related therapy options	Paracetamol; NSAIDs/COXIB with caution); Paracetamol + codeine	Biphosphomates; NSAIDs/COXIB; Paracetamol+weak/strong opioids.	Steroids, Gabapentinoids; Weak/strong opioids at low doses (moderate pain) strong short-acting opioids (severe pain) Tricyclic antidepressants	Gabapentinoids Weak/strong opioids, strong short-acting opioids if severe. Tricyclic antidepressants, NSAIDs- Steroids (with caution or contraindicate)

Abbreviations: NSAIDs, Non-steroidal anti-inflammatory drugs; NOA, New oral anticoagulants drugs; ASA, acetylsalicylic acid; NRS, Numerical rating scale; COXIB, COX-2 inhibitor.

Table III. The methodological Paradigm of rheumatological pain in some exemplary specific situations (cases report) to make the appropriate choice of the analgesic drug. The specialist bases the choice on a decision-making paradigm for the individual patient.

	Type of pain	Rheumatological pain paradigm				
		Chronic				
	Definition	Nociceptive-mechanical	Nociceptive-inflammatory	Neuropathic	Nociplastic	Mixed inflammatory/ neuropathic
Intrinsic pain factors	Descriptor	Persistent low back pain,	Persistent although with poor swelling, joint subluxation	Persistent, deaf, often positional, with sparesthesia	As subcontinuous, intense, meteosensitive, sensitive to stress sleep disorders, headache,etc.	Low back pain at rest with alternating sciatica,
	Cause of pathology pain	Chronic low back pain (with possible bone edema)	Chronic arthritis (RA, SPA)	Chronic sciatica	Primary fibromyalgia	Spondyloarthritis
Conditions to consider	Comorbidity	Heart disease and CKD contraindicate NSAIDs and COXIBs. Gastroenteropathies with gastroprotection	Heart disease and CKD contraindicate NSAIDs and COXIBs. Gastroenteropathies with gastroprotection Diabetes, Osteoporosis	S. Vertiginous orthost. hypotension	Chronic inflammatory arthropathy (secondary fibromyalgia),	Heart disease and IRC Gastroenteropathies with gastroprotection Diabetes, Osteoporosis
	Therapies in place	TAO, NSAIDs and COXIBs	With TAO, NSAIDs and COXIBs with caution	–	With TAO SSRI with caution	TAO FANS and COXIBs with caution
	Pain intensity assessment	Depending on NRS (if NRS ≥ 7 strong opioids)	Depending on NRS (if NRS ≥ 7 strong opioids)	Depending on NRS (if NRS ≥ 7 strong opioids)	Depending on NRS (if NRS ≥ 7 strong opioids)	Depending on NRS (if NRS ≥ 7 strong opioids)
Indications/ suggestions therapeutic class	Related therapy options	Paracetamol Bisphosphonates tramadol, strong opioids, NSAIDs-COXIB FKT	NSAIDs or COXIBs, low-dose Steroids, infiltration with steroids, weak or strong opioids	Gabapentinoids, carnitine, PEA, short-acting opioids, opioids with short half-life FKT	SSRI, benzodiazepines, amitriptyline, SAME body therapy FKT	COXIB, bDMARDS, Bisphosphonates Gabapentinoids short-acting opioids FKT

Abbreviations: NSAIDs, Non-steroidal anti-inflammatory drugs; NRS, Numerical rating scale; COXIB, COX-2 inhibitor; TAO, Oral anticoagulant therapies; SSRI, Selective serotonin reuptake inhibitor; bDMARD, Biologic disease-modifying anti-rheumatic drugs; FKT, Physio-kinesitherapy; CKD, Chronic kidney disease.

is most prominently involved in the perception of fracture pain. Immediate pain after a fracture is detected by mechanotransducers expressed by nociceptive fibers innervating the periosteum and is transmitted by A-delta fibers (Table I).

Pain in Orthopedic Pathology

The orthopedic pathology (net of traumatology and oncology) includes diseases with inflammatory, degenerative, metabolic, and mixed etiopathogenesis, at the expense of the spinal column, of the belts and of the upper and lower limbs. Pain in general is therefore nociceptive, inflammatory, pathological, that is nociplastic or neuropathic. Osteoarthritis of the large joints (hip, knee, ankle, shoulder and elbow) is now considered a degenerative inflammatory disease affecting the osteochondral unit. The degenerative paradigm no longer responds to the modern nosographic profile: therefore, the pain is not only related to cartilage degeneration, but also involves the subchondral and epiphyseal bone and requires a specific therapy. The lack of articular cartilage of the knee exposes the nociceptive endings of the subchondral bone that are stimulated by intense and supra-threshold stimuli, causing pain even in the absence of inflammation. Tendon-myopathies have a multifactorial etiology and a pathogenetic profile, in relation to the main site of suffering: enthesis, tendon body, myotendinous junction. Pain is acute when it is related to a trauma. It is slow, subtle, chronic when it appears on a phlogistic matrix, especially in a degenerative disease. Spinal diseases have a peculiar complexity due to the presence of the spinal cord in close contiguity with the skeleton. The algogenic sources are numerous, schematically represented by the myofascial structures (generally involved in all acute and chronic spinal pain syndromes), by the zygapophysial joints (with multifactorial pathogenesis), by the intervertebral discs (both as an autonomous structure and as a conflict with the neighboring root structures), and by the sacroiliac joints. The stimuli capable of inducing pain can be mechanical at the level of the Junghans motor segment, of the single districts with specific morphological peculiarities or at the level of the global structure of the rachis (frontal or sagittal deviations) and can be inflammatory or mixed. Osteoporosis is defined as a "silent epidemic" and the pain symptom belongs to its fracture complication, since it reveals its presence or sometimes unveils the never identified disease (Table II). In case of nociceptive/mechanical orthopedic pain, the pharmacological treatment suggested is based on paracetamol or paracetamol in association to codeine, in case of nociceptive inflammatory pain. Steroids, NSAIDs/COXIB (cycles) paracetamol in combination with weak/strong opioids and bisphosphonates are recommended for nociceptive-inflammatory pain, while steroids, tricyclic antidepressants SNRI (duloxetine), gabapentinoids, weak/strong opioids at low doses for a moderate pain, strong short-acting opioids for severe pain, anticonvulsants, and bisphosphonates are recommended as therapeutic approach for neuropathic pain. Finally, for pain related to mixed inflammatory and neuropathic forms NSAIDS/COXIB, steroids, tricyclic antidepressants SNRI (duloxetine), gabapentinoids, weak/strong opioids at low doses for moderate pain, strong short-acting opioids for severe pain, anticonvulsant pain, and bisphosphonates need to be considered.

Pain in Rheumatological Pathology

Pain in osteoarthritis (nociceptive-mechanical) typically arises at the beginning of the load or movement and then subsides with the "warming" of the joint. The recent new Osteoarthritis Research Society International (OARSI) guidelines of the American College of Radiology (ACR), European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), and European League Against Rheumatism (EULAR) recommend non-pharmacological therapy as a first-line approach, followed by topical NSAIDs and possibly NSAIDs with gastroprotection or COXIBS, intra-articular injections with steroids or hyaluronic acid, and clodronate or neridronate (if bone edema on MRI are present). Nociceptive-inflammatory pain is typically represented by chronic arthritis, an entity typically dominated by inflammation, with a disabling evolution, in which pain could be controlled with steroids (oral or infiltrative) and with the so-called "background" therapy (DMARDs, biotechnological drugs or Jak inhibitors), capable of modifying over time the natural history of the disease, aiming at clinical remission, which usually leads to a strong attenuation or absence of pain. It is at the beginning of treatment that opioids can take place, pending the effectiveness of the canonical treatment. Acute neuropathic pain finds a clear example of acute lumbosciatica that can be effectively treated with dexamethasone, peridural infiltrations, NSAIDs or COXIBs, opioids, and

with non-pharmacological therapies, in particular with TENS. Mixed inflammatory-neuropathic pain is typical of canalicular syndromes, often the first symptom of chronic arthritis, as with Carpal Tunnel Syndrome, which can usually be effectively resolved with steroid infiltrative treatment.

Chronic nociceptive-mechanical pain is exemplified by chronic low back pain in evolved spinal osteoarthritis that can be treated with gabapentinoids, medium-high-dose dexamethasone, and non-pharmacological measures. Literature data[13] show that opioids therapies are an effective adjuvant for the treatment of patients with moderate-to-severe chronic low back pain, but clinicians need to pay attention to adverse events such as opioid abuse, overdose, and other long-term effects[13]. However, new classes of opioid molecules are being developed with analgesic potential with a higher degree of tolerability, in order to avoid abuse[14].

The treatment of chronic (nociceptive-inflammatory) pain of inflammatory arthropathies passes on steroids, to be used at the minimum effective dosage and on the so-called "background" therapy, as already described. Spikes, especially initial, or during exacerbations, can be sedated with opioids (when NRS $\geq$ 7), with NSAIDs and COXIB. The chronic neuropathic pain of chronic sciatica assumes a typically discontinuous course: in these cases, rehabilitation and non-pharmacological physical therapies can once again give valid support to antidepressants (especially amitriptyline and SSRIs), gabapentinoids, carnitine, palmitoylethanolamide (PEA), alpha-lipoic acid, and in the phases of exacerbation short-acting opioids. Nociplastic pain is represented in rheumatology by fibromyalgia, a syndrome of widespread pain, often secondary to another rheumatic pathology. It is a disproportionate pain to the extent of the insult that produces it and that can last well beyond the stimulus (hyperalgesia and allodynia). The pain is often migrant, although usually localized in characteristic tender points, and is heavily affected by climatic variations, often associated with irritable bowel syndrome, restless legs syndrome, sleep disorders, and headache. In these patients, massage therapy, thermal mud, antidepressants, S-adenosylmethionine, and mind-body therapies are used. Finally, chronic mixed inflammatory-neuropathic pain is an example of spondylitis, typically inflammatory pathologies, characterized by disabling low back pain, especially at night with alternating severe sciatica. In these patients, the "background" therapy is represented by biotechnological drugs, but the role of etoricoxib is not negligible, for its prompt pain-relieving action, as well as the use of opioids, recently considered to be as good therapeutic options for this type of pain. Some cases of rheumatological pain are reported in Table III, following the flow of the paradigm concept.

Pain in Post-Surgery

Post-surgery pain is considered as a manifestation of acute pain. It is characterized by both inflammatory and neuropathic pain (called mixed pain); therefore, it is impossible to distinguish different pathologies and different types of pain drugs to treat them. Post-surgery pain is complex, and it cannot require only the use of opioids for its treatment. Orthopedic and traumatological surgery is characterized by a high incidence of severe pain, since the structures involved in surgery are rich in pain receptors. The pain induced by surgery generally triggers a "stress" reaction, resulting in an increase of cortisol, prolactin, aldosterone, glucagon, thus inducing a functional overload for vital organs. In surgery, chemical, mechanical or thermal stimuli cause tissue damage with consequent release of substances such as histamine, bradykinins, prostaglandins, serotonin, substance P, acetylcholine that stimulate nociceptors with the activation of the nerve impulse. Moreover, sensitization phenomena, induced by substances such as prostaglandins, reduce the threshold of stimulation. This phenomenon explains why the area damaged by trauma or surgery or both becomes easily sensitive even to low intensity stimuli. In addition to this, there is also the phenomenon of central sensitization, which is due to the action of neurotransmitters that activate other receptors with a reduction of their stimulation threshold. Typical examples are hyperalgesia at the site of surgical wounds and allodynia (e.g., the painful sensation for non-painful stimuli). Post-surgical pain is accompanied by muscle contractions close to the surgical site and a more general discomfort. In the post-operative period, especially in cases where general anesthesia is used, pain becomes alarming, progressive, and sometimes sudden upon awakening. Prolonged post-surgical pain is sometimes synonymous with a complication. This is the reason why central or peripheral sensitization must be treated with adequate pharmacological treatments, starting from NSAIDs, opioids for acute pain and drugs active to CNS to avoid central sensitization.

Peripheral sensitization of nociceptors leading to primary hyperalgesia is an important contributor to post-surgery pain. A multimodal approach is adopted in this type of pain. COXIB selective, nonsteroidal anti-inflammatory drugs and paracetamol (associated to strong and weak opioids) are used to reduce pain. Dexamethasone, an anti-inflammatory corticosteroid, is widely used in anesthetic practice to prevent nausea and vomiting. Other effects include an improvement of the quality of recovery and reduced fatigue.

As reported above, central sensitization plays a relevant role in the development of postoperative pain. The NMDA receptor ketamine, the alpha$_2$delta ligands pregabalin and gabapentin and the alpha$_2$-adrenergic agonist's clonidine and dexmedetomidine are drugs used to attenuate this state. Ketamine acts improving analgesia and it is mainly used for surgical patients who suffer from severe pain, for example after thoracic and upper abdominal and major orthopaedic surgery. Gabapentin, developed for the treatment of neuropathic pain, and alpha$_2$-adrenergic agonists act reducing pain intensity and opioid consumption.

Post-surgical pain, for its peculiar pathogenesis, intensity and specificity, finds the anesthesiologist as its protagonist, who also supports the various specialists in the management of the pain particularly resistant to oral or intravenous pharmacological therapies in different settings, with invasive procedures in day hospital or in ordinary hospitalization, such as pharmacological epidurolysis/pulsed radiofrequency, the diagnostic epiduroscopy with possible pharmacological lysis/RFP, the electrical spinal neuromodulation (SCS, Spinal Cord Stimulation) and the spinal drug neuromodulation (IDD, Intrathecal Drug Delivery).

Non-Pharmacological Therapy

Non-pharmacological treatments (NPT) for osteoarticular pain are a group of interventions strongly recommended as first line therapy by several international scientific organizations (ACR, OARSI, NICE, EULAR) for elderly patients affected by osteoarthritis (OA), in order to avoid drug-related side effects in patients with cardiovascular risks or with other relevant comorbidities[13,14]. NPT used in non-pharmacologic treatment for osteoarticular pain are listed in Table IV.

Interventional Techniques

Radiofrequency neurolysis is a technique used to reduce pain. The electrical energy produced by radio waves acts on a small portion of the nerve by reducing the transmission of pain signals from the specific area being treated. This can be achieved in two ways: with thermoablation (injurious radiofrequency), in which the area around the tip of the needle is heated to 75-90°C for a few seconds and thus a portion of the nerve is demolished; with neuromodulation (pulsed radiofrequency), with only an electrical effect on the nerve, not injurious, but effective and lasting. Radiofrequency is used to treat back pain, neck pain, arthrosis and pain coming from joints in general (hips, knees, shoulders, hands and feet), non-orthopaedic pain coming from nerves or their pathologies such as neuromas, neuropathies and some types of headaches. Among the various forms of chronic pain, low back pain, with an incidence of 65.5% in the population, represents one of the most frequent causes of absence from work and therefore has a high socio-economic incidence. Low back pain is defined as a pain syndrome localized in the lumbar region (space between the 12th rib and the gluteal groove), with or without projection of pain to the lower limbs. It is an extremely frequent disorder in adulthood, with maximum incidence in subjects over 50 years of both genders, and often require a multimodal approach, pharmacological and no-pharmacological treatments, for the management of pain.

80% of patients, treated with radiofrequency, obtain a satisfactory benefit for more than 12 months. After a few years, the pain may return, and the treatment may be repeated. Injury radiofrequency does not always provide a longer duration of wellness.

Radiofrequency is a safe and effective technique for treating pain, and it is generally very well tolerated. In experienced hands, complications are rare. Radiofrequency modifies the behavior of the nerve. Sometimes the benefit is immediate, but pain may recur; it is assumed that this is due to a phase of irritation of the treated nerve that can last up to 3-6 weeks. It is not possible to predict which type of patients will experience a resumption of the painful phase. For this reason, post-procedural algological controls are performed approximately after 4 weeks; 80% of treated patients obtain a satisfactory and lasting benefit.

Table IV. Non-Pharmacological Therapies used in non-pharmacological treatment for osteoarticular pain.

Non-pharmacological therapy	Function
Rehabilitation	Targeted exercises for the functional recovery of muscular strength and the restoration of the normal articular range of motion with consequent further reduction of pain[13-18].
Orthosis	Devices created to support a deformity of a part of the body, with the aim to help the patient to move easily (e.g., orthopaedic corsets for vertebral painful fractures, knee pads for joint instability, custom orthotics for limb length inequality, for the reduction of low-back, hip, knee and ankle pain)[19].
Pulsed Electromagnetic Fields	Stimulate the reduction of some inflammatory agents, such as IL-6, IL-8, PGE2 and COX-2, and increase the presence of anti-inflammatory molecules, such as IL-10 and A2A and A3 adenosine receptor[20,21].
Transcutaneous Electrical Nerve Stimulation (TENS)	Applied on the skin, activates mu and delta opioid receptors causing the release of endorphins. Peripheral neuropathic pain, such as sciatalgias, cervicobrachialgias, low back pain and fibromyalgia[22-26].
Extracorporeal Shock Wave Therapy (ESWT)	A mechanical stimulus that leads to collagen neosynthesis and neovascularization, used for the treatment of tendinopathies, enthesopathies and peri-articular soft tissues disorders[27,28].
Ultrasound	An effective reduction in knee osteoarthritis pain is suggested even if with a low quality of evidence[29].
Low Level Laser Therapy	Relieves pain in chronic non-specific low back pain, but with a lack of evidence in the functional recovery[30].
Acupuncture	Needles are inserted in a specific point to stimulate peripheral nociceptive A delta and C fibers, leading to peripheral and central pain control, but evidence of effectiveness in the treatment of acute low back pain, with a short duration (less than 3 months) are few[15,22].
Tai Chi	Reduces pain and disability in low-back pain patients by several different postures[15,31].
Yoga	Involves concentration, relaxation, breathing techniques and body postures, reduces low-back pain but with no statistically significant results[15,32].
Thermal Mud Therapy (MT)	The mud application is effective in reducing widespread pain in fibromyalgia patients, with long lasting results[33] and in improving the joints functions in knee and hand osteoarthritis[34]. Because of its application temperature, MT is contraindicated in case of inflammation[33].
Chiropractic	Lack of solid scientific concept at the basis of this method[35], except for back pain.
Massage Therapy	Small effects on short-term observed in case of low-back pain[22].
Behavioral Education	Exposition to vibrations, repetitive gestures, microtraumas, poor posture are causes of painful arthropathy. Weight control reduces the risk of knee and hip arthroplasty[36].

Abbreviations: TTENS, Transcutaneous Electrical Nerve Stimulation; ESWT, Extracorporeal Shock Wave Therapy; MT, Thermal Mud Therapy.

Conclusions

The therapeutic approach to osteoarticular diseases involves a clinical reasoning that considers both the diseases through a specialist diagnostic-therapeutic path in orthopedic, rheumatology or rehabilitation settings and patients' characteristics related multimorbidity and polytherapy.

From these considerations, the Paradigm approach arises, with the aim to reach the most effective pharmacological and non-pharmacological pain treatments. Pain therapy is not chosen according to a mere temporal sequence of different classes of analgesics and their effectiveness, but according to an appropriateness to the patient's complexity.

Opioids, for example, do not necessarily become the third prescriptive choice, after paracetamol and NSAIDs, but they can sometimes become the first choice, taking into consideration the intensity of the pain itself, all the therapies for comorbidities and the patient general state.

Osteoarticular pain can be described according to physiopathological mechanisms and specific descriptors, such as onset (sudden, slow, worsening), characteristics (cramp-like, uretic, pressing, constrictive, piercing, dull, etc.), course (intermittent, remitting, continuous), site (diffuse, circumscribed, radiated, variable), potential triggers (spontaneous or evoked), intensity (indicators of intensity, such as NRS, VAS or WOMAC should be added bio-psycho-social impact – psychological, social, quality of life). Conventionally, a treatment is believed to be effective if it reduces pain by at least 50%, with lasting relief.

In addition to the reduction of pain, depending on the specificity of the patient, the improvement of the quality of life, the functional evaluation and the reduction of the consumption of analgesic drugs must be considered. Combinated therapies (for instance, pharmacological and non-pharmacological therapies or pharmacological therapies and interventional techniques) could provide greater pain relief and fewer side effects, which are usually connected to higher single doses of a single therapy.

The General Practitioner manages the level of treatment that can be defined as "basic level", meaning the minimum and essential interventions. Otherwise, the assessment by the orthopedic-traumatologist, rheumatologist, neurosurgeon or physiatrist will be necessary for the specific diagnosis of osteoarticular or traumatic disease, considering the polymorphic clinical picture of each patient. This defines the osteo-articular pain treatment paradigm, which becomes the most relevant therapeutic target for both the clinician and the patient with osteoarticular disease − including other symptoms and clinical signs deserving medical attention. The osteoarticular pain treatment paradigm could lead to a personalized and safe treatment (pharmacological and non-pharmacological), taking into account each clinical element. This concept will bring back medical profession to its real duties: relief pain and care for the sick.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Data Availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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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