Musculoskeletal pain

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Abstract

Musculoskeletal pain affects different parts of the body (neck pain, limb pain, low back pain, joint pain, chronic widespread pain) and is a major reason for patient consultation. It mainly affects the elderly but can also affect other population groups regardless of age, gender, or economic status. It affects approximately 47% of the general population. It is mostly accompanied by emotional stress and a decline in physical function which affects the quality of life. Musculoskeletal pain can also lead to disability, decline in cognitive activity, falls and poor sleep. As much as musculoskeletal pain is associated with musculoskeletal conditions, healthcare practitioners should be aware that pain should be treated as a condition on its own and not only treat the underlying musculoskeletal conditions. Management includes both pharmacological and non-pharmacological approaches and it is important for healthcare practitioners to note that either approach might not be effective alone and a combination of approaches should be considered.

Keywords: musculoskeletal pain, muscle pain, bone and joint pain

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Introduction

Musculoskeletal pain is defined as pain affecting the muscles, joints, bones or related soft tissues.[1] The most common types of musculoskeletal pain include chronic low back pain, neck pain and pain linked to osteoarthritis and rheumatoid arthritis. However, it also includes muscle sprains, pain from fractures, shoulder pain and other.[2] According to the World Health Organization (WHO), 20–33% of the world's population has some form of chronic musculoskeletal pain, translating to 1.75 billion people globally.[3] Lehti et al.[4] reported 57–61% of patients that indicated having intermittent or daily musculoskeletal pain. Musculoskeletal pain can be acute or chronic, with chronic pain classified as primary or secondary.[5] Chronic musculoskeletal pain is long-term and accompanied by significant emotional distress or disability, without a clear disease-related cause. In contrast, chronic secondary musculoskeletal pain results from an underlying disease and may be associated with chronic inflammation due to infection, autoimmune processes and crystal deposition, musculoskeletal structural changes and neurological conditions like Parkinson's disease.[6] Inadequately managed musculoskeletal pain can adversely affect the quality of life of the patients and impose significant socioeconomic problems.[2]

Pathophysiology

Musculoskeletal pain is a multidimensional condition arising from dynamic interactions between peripheral and central nervous system mechanisms.[7] Peripheral sensitisation occurs following tissue injury, wherein damaged cells release pro-inflammatory cytokines—such as interleukin-1β (IL-1β) and tumour necrosis factor-alpha (TNF-α)—alongside chemical mediators like prostaglandins (PGs) and bradykinin.[8] These substances activate the sensitising sensory afferent fibres (Aδ, C-fibres), which act as high threshold mechanoreceptors, responding to high intensity mechanical stimuli.[9] This further awakens the silent nociceptors located in muscles, joints, ligaments, and tendons.[10] Activation of the silent nociceptors results in hyperalgesia (increased pain from noxious stimuli) and allodynia (pain from non-noxious stimuli).[11]

Prolonged nociceptive input can lead to central sensitisation, a phenomenon characterised by heightened excitability of neurons in the spinal cord's dorsal horn and altered pain processing in higher brain centres. This state amplifies pain perception, even after the initial injury has resolved. Dysfunctional descending pain modulation, involving structures like the periaqueductal grey (PAG) and rostral ventromedial medulla (RVM), further exacerbates pain. Normally, these systems suppress pain signals, but their dysregulation results in prolonged and exaggerated pain responses.[12]

Neurotransmitters such as substance P, CGRP and purinergic receptors, P2X3 amplify pain signals.

In skeletal system, adenosine triphosphate (ATP) released during trauma or other pathological processes binds purinergic receptors to excite nociceptive fibres. ATP is pain transducer in skeletal system.[13] In an acid-induced model of muscular pain, ASIC3 channels have also been shown to contribute to the development of mechanical hypersensitivity in this manner.[14]

In chronic pain states (pain occurring over three months), the immune system maintains ongoing pain through autoimmune mechanisms. Peripheral and central mast cells likely play a crucial role in the shift of acute to chronic pain by interacting with other immune cells and somatosensory nerve terminals.

Persistent peripheral inflammation and central plasticity lead to maladaptive changes, such as ectopic sympathetic nerve

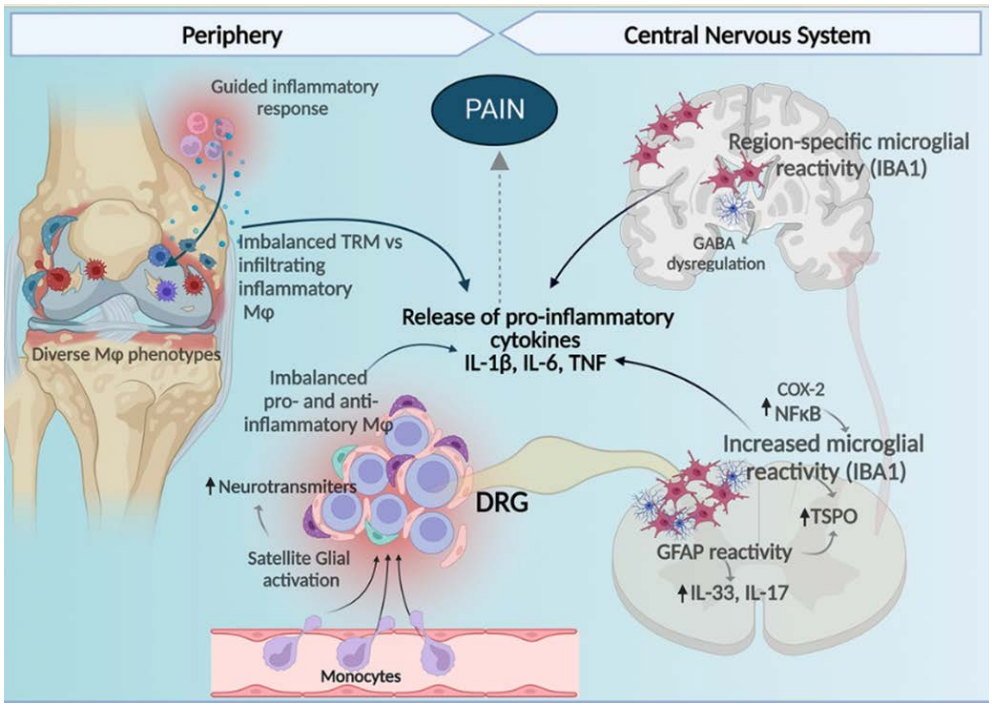

Figure: Interaction between the peripheral and central nervous system mechanisms during inflammation[15]

sprouting in joints contributing to prolonged pain and disability. Moreover, psychosocial factors such as anxiety, depression, catastrophising, and social context have been shown to influence pain perception and recovery trajectories.

Clinical manifestation

Musculoskeletal pain manifests as a tight, radiating, diffuse and drilling sensation.[16] It is usually nociceptive in nature but can be neuropathic, especially in the elderly.[17] Pain arising from the joints is more localised than that affecting the muscles (myalgia) and is known to worsen at night. Both myalgia and joint pain are greatly affected by movement as compared to bone pain, and bone pain worsens at night. Deep-tissue hyperalgesia is often widespread and difficult to differentiate from pain from other tissues.[16]

The pain can be acute or chronic, diffuse or focal (even multifocal), in musculoskeletal or associated neural tissues.

Clinical symptoms include:

- Local symptoms of pain or widespread and persistent pain or peripheral nerve irritation which may eventually lead to decreased nerve conduction velocity.
- Weakness, such as reduced finger or grip strength.
- Limited motion and stiffness.

Symptoms progressively increase with greater tissue injury and inflammation in affected anatomical sites. Symptoms are exacerbated by work-related or personal stress, for example, poor control over one's work, difficult relationships and time pressure. Symptoms have diurnal fluctuation. At first, symptoms subside with cessation of work (i.e. between shifts, overnight, over weekends, and during vacations). As exposure persists and tissue injury progresses, symptoms may be insufficiently alleviated by rest.[18]

Management

Management of musculoskeletal pain can be divided into two types, pharmacological and non-pharmacological. The non-pharmacological treatment option has home exercises for mild pain and transcutaneous electrical nerve stimulation, acupuncture and ultrasound for severe pain. Aerobic training and muscle strengthening are reported to improve pain and physical activity.[19] Cryotherapy, also known as cold therapy, is applied directly to an injured area to reduce haemorrhage and vasodilation, decreases the local inflammatory response, oedema production, and pain perception.[20] Therapeutic heat is often applied alongside prolonged stretching to help alleviate musculoskeletal contractures, joint stiffness, and chronic inflammatory conditions, ultimately reducing pain and improving mobility and function. In cases of subacute and chronic pain, heat therapy enhances collagen flexibility, boosts blood circulation and metabolic activity, and supports the resolution of inflammation.[21] Transcutaneous electrical nerve stimulation therapy (TENS) works by delivering low-voltage electrical impulses through electrodes placed on the skin. These impulses help block pain signals from reaching the brain and stimulate the release of endorphins, the body's natural painkillers.[22]

Acupuncture is an ancient Chinese therapy practised for more than 2 500 years to cure disease and relieve pain. It depends on the use of thin metal needles that are inserted into specific body sites and stimulated manually or electrically. Acupuncture is considered an invasive procedure and needs a professional physician or practitioner to perform it.[21]

Table I: Musculoskeletal pain types and their management

Musculoskeletal pain	Types or associated conditions	Manifestation	Non-pharmacological management	Pharmacological management
Muscle pain	Cramps Lower back pain Neck pain	Pain, soreness and swelling	Stretching the affected muscle	Vitamin E
Bone pain	Fractures	Severe pain	Bone stabilisation and minimal bed rest	NSAIDs and COX-inhibitors
Joint pain	Gout	Extreme pain, swelling, tenderness, redness and local heat	Hydration, avoid excessive alcohol consumption and purine containing food such as liver, rest and immobilisation	Allopurinol, Colchicine, NSAIDs and glucocorticoids
	Rheumatoid arthritis	Symmetric pain, swelling, joint tenderness, muscle weakness	Physiotherapy, occupational therapy	NSAIDs and corticosteroids
	Osteoarthritis	Stiffness, pain and motion limitation	Physical therapy, joint protection and splinting, and weight reduction	Paracetamol and aspirin
Tendon/ligament pain	Sprains and strains	Pain, immobilisation	Cryotherapy and early ambulation	NSAIDs
	Tendinitis	Pain and swelling	RICE	NSAIDs

Patient's education about their condition helps in non-pharmacological treatment strategies, such as physical activity, rest and exercise.[21] A comprehensive patient assessments including detailed history taking with neuroimaging may be necessary to treat well.

The types of musculoskeletal pain, their presentations, and management strategies are shown in Table I.[23-28]

Pharmacological treatment is the mainstay for the management of pain. A wide range of analgesics have been used in the treatment of musculoskeletal pain. The WHO analgesic ladder has guided the treatment in these patients.[29]

Non-opioid analgesics

Paracetamol

Paracetamol is thought to act both centrally and peripherally. It reduces prostaglandin synthesis from arachidonic acid via inhibition of the cyclooxygenase isoenzymes COX-1 and COX-2.[30] It is used in combination with nonsteroidal anti-inflammatory drugs (NSAIDs). Paracetamol is relatively effective in many pain conditions, and it has minimal adverse effects. However, regular monitoring for hepatotoxicity is required for patients who receive this drug for longer periods at high doses.

Nonsteroidal anti-inflammatory drugs

NSAIDs are widely used for the treatment of musculoskeletal pain.[31] They have analgesic and anti-inflammatory properties and may be used for the treatment of mild-to-moderate pain. These drugs work by blocking cyclooxygenase (COX), an enzyme responsible for the production of prostaglandins (PGs), which are strong inflammatory mediators. Traditional NSAIDs, however, inhibit both COX-1 and COX-2 isoforms and have been linked to serious gastrointestinal adverse effects such as ulcers and an increased risk of bleeding.[32] Prolonged use of NSAID treatment is also associated with other adverse effects including inhibition of platelet function and increased bleeding time, as well as bronchospasm following the administration of aspirin and other NSAIDs in some patients with asthma.

Topical NSAIDs, like topical diclofenac, are effective for reducing musculoskeletal pain and should be considered in the treatment of patients with musculoskeletal pain, particularly for those who cannot tolerate oral NSAIDs.

COX-2 selective inhibitors (COX-2)

COX-2 selective inhibitors refer to a class of analgesic and anti-inflammatory drugs. COX-2 is found in inflammatory cells, tissue damage, synovia of joints, endothelium, and the CNS.[21] These drugs have the same effectiveness as the other NSAIDs with fewer side effects on the gastrointestinal tract. However, long-term use has been associated with increased risk of cardiovascular side effects and this should be taken into account especially in cardiac and susceptible patients.[33]

Opioids

Opioids produce their effect by acting as agonists at opioid receptors, which are found in the brain, spinal cord, and sites outside the CNS. There are three types of opioid receptors: mu (l), delta (d), and kappa (j).[34] It is important to know that opioids are not the first-line therapy for musculoskeletal pain because of the side effect profile and dependence. The side effects range from respiratory depression, sedation, nausea/vomiting, and constipation.[21] The overuse and overdose can also lead to coma and death. A study by Tlali et al.[35] examined the diagnosis and treatment of opioid-related disorders in a South African private sector medical insurance scheme. Their findings showed that the incidence of people diagnosed with or treated for an opioid-related disorder in the private sector is increasing rapidly.

Table II shows pharmacological agents used in the management of musculoskeletal pain and common side effects.[36,37]

Table II: Pharmacological agents used in the management of musculoskeletal pain

Class	Examples	Drug interactions	Common side effects
Non-opioid analgesics	Paracetamol	Warfarin, anticonvulsants, rifampicin, probenecid and chloramphenicol	Rash, hypersensitivity reactions such as urticaria, nausea and hepatotoxicity
NSAIDs	Aspirin Ibuprofen Diclofenac	Warfarin, probenecid, beta-blockers, diuretics and corticosteroids	Gastric effects ranging from mild irritation to erosion, peptic ulceration and bleeding
COX2 inhibitors	Celecoxib Etoricoxib	Diuretics, aspirin, oral contraceptives and ciclosporin	Risk of cardiovascular events and low incidence of diarrhoea, dyspepsia and abdominal pain
Opioids	Tramadol Morphine	Alcohol, antidepressants, antipsychotics and warfarin	Respiratory depression, sedation, nausea/vomiting and constipation
Anticonvulsants	Carbamazepine Gabapentin	Oral contraceptives, isoniazid, alcohol and diuretics	Drowsiness, ataxia, CNS depression and dizziness
Antidepressants	Amitriptyline Nortriptyline	MAOIs, SSRIs, anticholinergics, alcohol and other CNS depressants	Sedation
Muscle relaxants	Baclofen	Levodopa, CNS depressants, morphine, lithium and antihypertensives	Dizziness, fatigue and weakness

Adjuncts analgesics

Anticonvulsants

These drugs are used to treat seizures, however they can be used for neuropathic pain in musculoskeletal pain. Gabapentin and pregabalin are effective for the treatment of patients with neuropathic pain and work by inhibiting neurotransmitters within the cerebral cortex, which maintains the inhibitory tone necessary for counterbalancing neuronal excitation and decreasing the pain.[38] They bind to the a2-d-subunit of neuronal voltage-gated calcium channels and thus reduce the influx of calcium ions in hyperexcitable neuronal states. Although the side effect profile is tolerable at recommended doses, there is recent concern of respiratory depression when this medication is used in conjunction with CNS depressants, including opioids, and in patients with baseline respiratory impairment.[21]

Carbamazepine has also been used in musculoskeletal pain. However, the FDA approved indication is for neuropathic pain and trigeminal neuralgia. Carbamazepine blocks voltage-gated sodium channels that are mainly expressed in peripheral C and Aδ nerve fibres. Dysfunction of these small, un- or thinly myelinated fibres is associated with several chronic pain disorders, including small fibre neuropathies and fibromyalgia. However, muscle pain is nociceptive and the mechanism of this drug in management of this pain is not completely unknown.[39]

Antidepressants

Tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, provide pain-relieving effects that are separate from their mood-enhancing properties. Their analgesic action is associated with their ability to block calcium channels, inhibit sodium channels, and antagonise NMDA receptors.[40] More specifically, the analgesic effect is believed to be due to the presynaptic reuptake inhibition of monoamines such as serotonin and norepinephrine.[21]

Musculoskeletal drugs

The most commonly used muscle relaxant drug is baclofen. Baclofen is an agonist for gamma-aminobutyric acid (GABA) B receptors on pre- and postsynaptic neurons in the CNS and peripheral nervous system. Agonism of GABAB receptors found on type Ia presynaptic neurons arising from extrafusal muscle spindles causes an efflux of potassium (K+) leading to hyperpolarisation of the neuronal membrane, as well as decreased calcium (Ca2+) influx at presynaptic nerve terminals.[41] Baclofen therapy is associated with potential complications, including life-threatening toxicity and withdrawal syndrome.[21]

Conclusion

Musculoskeletal pain is a collective term for a variety of conditions which can also be secondary to other conditions. It can cause a burden on the quality of life of the patients and needs to be attended to. There are several non-pharmacological methods that can be used, however most patients end up taking medication to help reduce and manage the pain. NSAIDs are the drugs of choice but every patient needs to be treated as an individual to optimise therapy and ensure that they are getting the best help. Then the patients should be monitored for any potential side effects to the drugs.

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