The management of muscle pain

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Abstract
Muscle pain, also known as myalgia, is most commonly associated with sprains or strains. It frequently presents as redness at the site of injury, tenderness, swelling and fever. Muscle pain may occur as a result of excitation of the muscle nociceptor due to overuse of the muscle, viral infections or trauma. The most important endogenous substance released in response to the damaged tissues or nociceptor nerve endings with regard to muscle pain is adenosine triphosphate (ATP). Optimal pain management involves a combination of non-opioid analgesics, opioid analgesics, adjuvants, as well as non-pharmacological strategies. Non-opioid analgesics include paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, which are indicated for mild to moderate pain. Moderate to severe pain, on the other hand, requires opioid analgesics. This article provides an overview of muscle pain, and the management and treatment thereof.

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Key Summary Points
• Muscle pain, known as myalgia, can be in one targeted area or across many muscles, as a result of overexertion or overuse of these muscles.
• Pain can be classified as acute or chronic pain and further categorised as nociceptive or neuropathic.
• Causes of muscle pain include stress, physical activity, infections, hyper- or hypothyroidism.
• Sprains and strains are the most common types of muscle pains.
• Optimal pain management involves utilising a combination of non-opioid analgesics, opioid analgesics, adjuvants and non-pharmacological strategies.

Introduction
Muscle pain, medically known as myalgia, can be described as pain that originates in any muscle of the body. The pain can be in one targeted area or across many muscles, usually as a result of overexertion or overuse of these muscles.

“Pain, like love, is all consuming: when you have it, not much else matters, and there is nothing you can do about it. Unlike love, however, we are actually beginning to tease apart the mystery of pain.”¹

Myalgia may also occur without primary trauma and this is frequently associated with a viral infection. The severity of pain can range from mild to severe, depending on the cause. It can typically be described as cramping and aching. Signs and symptoms associated with muscle pain include redness at the site of injury, tenderness, swelling and fever.²

Classification of pain
Pain is classified according to its duration and pathogenesis. Depending on the duration of the pain, it can either be classified as acute or chronic.

Acute pain
This type of pain usually arises after obvious tissue damage and is therefore nociceptive in nature. The pain can be clearly located and resolves upon healing. It has a protective nature as it distinctly warns the individual of harmful situations.³

Chronic pain
Chronic pain usually persists from months to years. The intensity of the pain no longer correlates with the causal stimuli as there are changes to the nerve function and transmission. The pain loses its protective and warning signs and thus serves no purpose.³

This pain can either be classified as nociceptive or neuropathic.⁴

• Nociceptive pain
Nociceptive pain is known as a very high threshold pain that is activated in the presence of stimuli. It is the normal physiological pain that is associated with a warning signal that something is threatening the person's bodily tissues. It is felt when a person comes into contact with a stimulus, for example hot, cold or sharp. Nociceptive pain acts as a physiological protective system and signals when there is impending tissue damage. It requires
immediate attention and action, such as immediately pulling your hand off a hot plate. Sprains and/or strains, broken bones, lower back pain from disc disease or injury, and burns are examples of nociceptive pain.¹,⁴,⁵

• Neuropathic pain

Neuropathic pain is considered to be maladaptive and is a disease state of the nervous system. This type of pain occurs after there is damage to the nervous system. It is experienced due to the transmission of pain signals in the absence of actual tissue damage or inflammation, as found in fibromyalgia, tension headaches and irritable bowel syndrome. This pathological pain occurs when there are heightened sensory signals in the central nervous system and a low threshold of pain.¹,⁴,⁵

Causes of muscle pain

Muscle pain can be caused by stress, tension or physical activity. Some medical conditions known to cause muscle pain include⁶-¹⁰:

- Infections
- Hyper- or hypothyroidism
- Hypokalaemia
- Autoimmune conditions e.g. lupus
- Side-effects of certain medications (e.g. statins)

Pathophysiology of muscle pain

Muscle pain may occur as a result of excitation of the muscle nociceptor due to overuse of the muscle, inflammation and/or trauma. When the impact has occurred, endogenous substances are released in response to damaged tissue or nociceptor nerve endings. Some of these substances include¹¹:

- Potassium ion
- Prostaglandin E₂
- Bradykinin
- Serotonin
- Neuropeptides e.g. substance P
- Somatostatin
- Adenosine triphosphate

Of all substances released the most important one involved in muscle pain is adenosine triphosphate (ATP) which is released from muscle cells at high concentrations after damage to the muscles. The increased levels of substances released from the damaged tissue stimulate the nociceptors directly. The pain experienced during movements of these damaged tissues is as a result of the low threshold of sensitised muscle nociceptors.¹¹-¹³

In the case of muscle inflammation, the level of substance P and nerve growth factor (NGF) increases, which in turn leads to hyperalgesia known as increased sensitivity to painful stimuli in the affected muscle.¹¹,¹³

Sprains and strains are the most common types of muscle pain and are especially frequent in the elderly. Sprains occur as a result of overstretching of the ligaments. This can be caused by twisting of joints. The most regularly affected parts of the body are the ankles and wrists. This is usually followed by pain, swelling and at times bruising. Strains, on the other hand, are caused by the overstretches of muscles or tendons.⁴,¹⁴

Management of muscle pain

Non-pharmacological management

The non-pharmacological treatment of muscle pain is illustrated in Figure 1.

Treatment modalities include the following:

- Transcutaneous electrical stimulation (TENS)

TENS is a non-invasive procedure used in rehabilitation to modulate pain.¹⁵ Electrical currents are delivered through the skin to activate central inhibitory pathways decreasing central excitability. Activation of the descending inhibitory pathways from the midbrain and brainstem leads to inhibition of the nociceptive neurons in the spinal cord. This is used for acute and chronic pain.¹⁶-¹⁷

- Acupuncture

Acupuncture is a traditional Chinese-based therapeutic method which involves the insertion of small, solid needles into specific points in the body in order to improve health or modify painful states.¹⁸ There are several postulated mechanisms of action. Acupuncture is indicated for chronic pain unresponsive to standard therapy. Acupuncture may work via the same mechanisms as other complementary therapies (placebo, diversion etc).¹⁹

- Thermal modalities

Thermotherapy is the therapeutic use of heat, usually greater than that of body temperature, applied to the body.²⁰ Thermal modalities are classified as superficial thermotherapy (the application of a device that is used primarily to heat structures to
Pharmacological management

Optimal pain management involves utilising a combination of non-opioid analgesics, opioid analgesics, adjuvants and non-pharmacological strategies. The approach must be adapted such that it is possible in resource-limited areas as well. Treatment guidelines should therefore consider the acute and chronic phase of the pain state, and recommend the appropriate pharmacological or non-pharmacological treatment using evidence-based recommendations. They should also indicate when a single mode of treatment is appropriate and when multiple modes are required.21-23

The multimodal approach to pain management involves administering two or more analgesics with different mechanisms of action. The routes of administration may also be different. This approach is aimed at providing a synergistic analgesic effect using the lowest possible doses of these medications than if they were used alone.24

Non-opioid analgesics

The following non-opioid related medicines are available for managing pain: paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs), for example naproxen, ibuprofen and mefenamic acid. They adequately treat mild pain and moderate-to-severe pain in combination with other medicines, particularly opioids, to provide more effective relief and reduce adverse effects.25

Paracetamol

Paracetamol is one of the drugs of choice in pain management due to its excellent safety profile and lack of any significant side-effects.26 It acts as a prodrug, with an active cannabinoid metabolite. In the brain and spinal cord, paracetamol follows deacetylation to its primary amine (p-aminophenol) which is conjugated with arachidonic acid to form N-arachidonolylphenolamide, a compound known as an endogenous cannabinoid. The involved enzyme is fatty acid amidohydrolase. N-arachidonolylphenolamide is an agonist at the Transient Receptor Potential Cation Channel, Subfamily V, Member 1 (TRPV1) receptors and an inhibitor of cellular anandamide uptake, which leads to increased synthesis of endogenous cannabinoids, inhibiting cyclo-oxygenases in the brain at concentrations that are probably not attainable with analgesic dosages of paracetamol. It is of interest to note that a cannabinoid-1 receptor antagonist, given at a dosage level that completely prevents the analgesic activity of a selective cannabinoid receptor agonist, completely inhibits the analgesic activity of paracetamol as well. This fact allows us to explain the mechanism of action of paracetamol in more detail. Despite this finding, however, the definite proof that the analgesic and antipyretic effects of paracetamol are dependent on COX-inhibition is still unclear. Hence, it works effectively when combined with codeine for more effective control of moderate-to-severe pain and discomfort.27

NSAIDs competitively inhibit the cyclo-oxygenase (COX) enzyme; COX enzymes facilitate the bioconversion of arachidonic acid to inflammatory prostaglandins (PG). This results in the blockade of prostaglandin synthesis and subsequently dampened inflammatory responses.28-30 COX-1 and 2 are isozymes that only vary genetically. NSAIDs have three pharmacologically preferred attributes i.e. analgesic, anti-inflammatory and anti-pyretic activity. They generally have similar analgesic properties but selection is based on their receptor selectivity. COX-1 receptor activation produces gastric effects that mediate hypersecretion of gastric acid, thinning of the lumen and propagate the development of gastric ulcers. These medicines have various formulations.31

The only over-the-counter (OTC) available pain medications are aspirin (S0) and paracetamol (S2) and require no prescription. The NSAID ibuprofen is S2 when intended for the treatment of post-traumatic conditions such as pain, swelling and inflammation, for a maximum period of five days without a prescription. All other NSAIDs are S3 and can only be obtained via a prescription from a physician (Act 101 of 1965).32

It is important to note that NSAIDs have ceiling analgesic effects but the cyclo-oxygenase-2 mediated anti-inflammatory effects are dose dependent.33 COX-2 is not detected in most normal tissues, but its expression is rapidly induced by stimuli such as proinflammatory cytokines (IL-1b, TNFα), lipopolysaccharides, mitogens and oncogenes (phorbol esters), fibroblast growth factor, epidermal growth factor, luteinising hormone, (LH) and fluid-electrolyte haemostasis, resulting in increased synthesis of PG in inflamed and neoplastic tissues.29

The NSAIDs such as aspirin, ibuprofen, diclofenac, ketorolac and mefenamic acid, have analgesic and anti-inflammatory properties, which are useful in the management of pain.27

Ibuprofen is one of the most frequently used NSAIDs for mild and moderate pain.34 It has gained advantage in the market and is available as an OTC medication for fever reduction, as well as pain relief. Studies have shown ibuprofen to be superior in terms of its safety profile, compared to ketorolac. However, ketorolac has been used as a single agent for the treatment of postoperative pain, especially when used as an adjuvant to opioid analgesia.35

If pain is constantly present, analgesics should be administered on a regular time schedule, i.e. ‘by the clock’, whereby the medicine is administered at a fixed time interval with dosages tailored according to the patient’s pain, with the next dosage given before peak time effect of the previous dosage has worn off. This will
result in a more predictable and consistent level of analgesia.23,25
Aspirin and paracetamol are very popular as OTC pain medication.1
Selection of an analgesic is determined by the side-effect profile
and severity of pain.

Opioid analgesics

Opioid analgesics provide analgesia for moderate to severe pain
for the vast majority of patients and with a wide margin of safety.37
This group includes the following examples: codeine, morphine,
oxycodone, methadone, fentanyl and pethidine. Opioids can be
divided into weak and strong opioids. Weak opioids are used alone
or in combination with other analgesics, in the management of
moderate pain. Strong opioids are usually reserved for severe pain.1

Opioids are the third step in the pain treatment ladder and the
recommended treatment of moderate or severe pain.38 One of
the undesirable effects of opioids which is of great concern in
health care is dependence, which is associated with prolonged
use. Concomitant administration of an opioid with ibuprofen can
reduce the amount of opioid analgesic required for pain control.

- Pethidine, morphine and fentanyl

A variety of opioids are available for use; however, there is
insufficient evidence to support a preference of one opioid over
another.39-40 Pethidine does not provide good analgesia compared
to morphine and should not be used long-term because of the
possible accumulation of its toxic metabolite, norpethidine, that
can result in seizures. Fentanyl provides approximately equal
analgesic effects as morphine, and can be used for rapid analgesia
over short periods of time if morphine is contra-indicated. Opioids
are the most commonly administered intravenous agents for
moderate to severe pain. The opioid dosage that effectively
relieves pain can differ, and should be based on a pain severity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Dosages</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Tablets, suppositories, intravenous solutions</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>1–4 g/daily 1 g q 6 hourly</td>
<td></td>
<td>Hypersensitivity skin reactions: neutropenia, thrombocytopenia, nephrotoxicity, hepatotoxicity</td>
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<tr>
<td>Non-specific NSAIDs:</td>
<td></td>
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<tr>
<td>Ibuprofen</td>
<td>Tablets, topical patch, topical gel, oral syrup</td>
<td>200–400 mg q 4–6 hourly</td>
<td>Same as for diclofenac</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Capsules</td>
<td>25–50 mg q 6–8 hourly</td>
<td>CNS effects: dizziness, drowsiness, mental confusion, headache in less than 10% of patients, corneal deposits</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Tablets</td>
<td>200 mg daily with food</td>
<td>Same as diclofenac</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Tablets, intramuscular injection, topical gel, suppositories, topical patch</td>
<td>Oral: 25–50 mg q 8 hourly, to maximum of 150 mg/day Intramuscular: 75 mg q 12 hourly, maximum of 150 mg/day for 2 days only Suppositories: 100 mg daily</td>
<td>GIT: gastric erosion, peptic ulceration Hypersensitivity reactions: skin rashes, pruritus and angioedema, renal toxicity</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Tablets, topical gel</td>
<td>40 mg/day</td>
<td>Same as diclofenac</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Tablets</td>
<td>500 mg q 12 hourly</td>
<td>Same as diclofenac</td>
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<tr>
<td>Mefanemic acid</td>
<td>Oral syrups, tablets, suppositories</td>
<td>500 mg q 8 hourly</td>
<td></td>
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<tr>
<td>COX-2 inhibitors:</td>
<td></td>
<td></td>
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<tr>
<td>Celecoxib</td>
<td>Tablets, capsules</td>
<td>100–200 mg q 12 hourly</td>
<td>GIT: nausea, dyspepsia, diarrhoea, flatulence, Steven-Johnson’s syndrome Hypersensitivity reaction: toxic epidermal necrolysis, renal toxicity</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>Tablets, capsules</td>
<td>60–90 mg q 12 hourly</td>
<td>Same as for celecoxib</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Tablets, capsules</td>
<td>7.5 mg q 12 hourly or 15 mg daily</td>
<td>Same as for celecoxib</td>
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</table>
assessment. However, the long-term use of opioids is associated with constipation; therefore, a combination of a stool softener and stimulant laxative can be used as prophylaxis when it is anticipated that these agents will be used over an extended period of time.39-40

Morphine is well established as the first-line strong opioid and is available in both immediate-release and prolonged-release formulations. Immediate-release tablets are used to individualise patient dosages and have an adequate dosage for pain control. Prolonged-release oral formulations improve patient compliance by allowing longer dosing intervals. Oral morphine solution is usually used for persistent pain and when patients are unable to swallow tablets.40

The use of a pain scale to manage pain is a crucial part of effective opioid therapy because these medicines do not have a so-called ceiling effect. Therefore it is imperative to ensure an appropriate dosage that provides effective analgesia with manageable side-effects. A suitable opioid antagonist, such as naloxone, should also be available for the management of adverse effects or opioid-related complications.23

When pain management is no longer needed, slow withdrawal of opioids may be necessary to prevent abstinence syndrome, with continuous monitoring of vital signs. This may require tapering the daily dosage whilst monitoring the level of pain, and with continuous reassessment to ensure that the patient remains pain free.40

Combination opioid formulations

When pain management by paracetamol and NSAIDs is inadequate, combination agents are usually employed. Hydrocodone and oxycodone have been increasingly used in combination with paracetamol.38 These agents proved to be more effective in postsurgical injuries and exhibit increased pain relief compared to single usage of NSAIDs. Caution is indicated in patients that have a previous problem with drug abuse and seizures as some patients on antidepressants (SSRIs, MOA) have experienced seizures with concomitant use of these agents.31

Adjuvant therapy

Adjuvant therapy is sometimes necessary to manage the side-effects of pain medication, provide symptom relief, treat anxiety and manage related or underlying conditions. This is because patients with chronic pain are more likely to report anxiety, depression, neuropathic pain and significant activity limitations. Examples of adjuvant medicines include corticosteroids, anxiolytics, antidepressants, hypnotics and anticonvulsants/antiepileptic agents.23,41

A step-wise approach

The World Health Organization’s (WHO) ‘analgesic ladder’ serves as the mainstay of treatment for the relief of pain together with psychological and rehabilitative modalities. This multidimensional approach offers the greatest potential for maximising analgesia and minimising adverse effects.23,41

According to the WHO, the key concepts to the effective management of pain are as follows23,41:

- **By mouth:** If possible analgesics should be given by mouth.
- **By the clock:** Analgesics should be given at fixed time intervals and the dosage should be titrated according to the patient’s pain, and the next dose should be given before the previous dose has fully worn off.
- **For the individual:** The choice and dosages of the analgesics should be tailored to the needs and circumstances of the particular patient.
- **By the ladder:** The well-known WHO ladder, illustrated in Figure 2, advocates a step-wise approach to the use of analgesics, as explained below.
Step 1: Non-opioids (e.g. aspirin, paracetamol or ibuprofen) are used for mild to moderate pain.

Step 2: Weak opioids (e.g. codeine phosphate, dihydrocodeine, tramadol and buprenorphine) are recommended for moderate pain, used alone or in combination with one of the non-opioids mentioned in step 1.

Step 3: Strong opioids (morphine, hydromorphone, oxycodone, buprenorphine and tapentadol) may be used alone or in combination with a non-opioid (from the first step) for severe pain.

If the patient’s pain is already severe, it is recommended that the physician move to the third level of the ladder immediately, rather than starting with the first two.

As illustrated by Figure 2, opioids play an important role in the management of, not only acute and chronic pain, but also in the management of moderate to severe pain.23,41

However, certain barriers limit the effective use of opioids in the management of pain:

• Concerns about the use of opioids from healthcare workers, family members and patients; these concerns may be related to the side-effects and risk of dependence when using opioids.

• Development of tolerance to the chronic use of opioids.

In instances where muscle pain does not subside with the use of mentioned analgesics, an alternative interventional therapy is muscle relaxants, where the relief of muscle spasms may also reduce pain and discomfort.41

Skeletal muscle relaxants are classified into two main categories namely, antispasticity and antispasmodic medications. Antispasctic medications (e.g. baclofen) acts on the spinal cord or on the skeletal muscles itself to better muscle hypertonicity and involuntary spasms. Antispasmodic medications lessons muscle spasms through alterations of central nervous conduction. These agents are divided into benzodiazipines and nonbenzodiazipines.41

A new skeletal muscle relaxant in South Africa is Myprocam®. The active ingredient is cyclobenzaprine, a nonbenzodiazipine antispasmodic agent, which blocks nerve impulses recognized as pain. Cyclobenzaprine is structurally related to the tricyclic antidepressants, like amitriptyline and nortriptyline. It is categorized as a muscle relaxant with a mechanism of action not fully understood, but is thought to be an agonist of the α2 receptor at the descending noradrenergic neurons within the supraspinal area of the brain stem. Some evidence also revealed serotonergic antagonism of the 5-HT2 receptors.41-42

Myprocam® is often combined with analgesics like ibuprofen or naproxen and is used in addition to rest and physical therapy for short-term relief of muscle spasm associated with acute, painful musculoskeletal conditions. The recommended adult dose is a 15 mg capsule, taken once daily. Some patients may require up to 30 mg per day, administered as one Myprocam® 30 mg capsule, taken once daily, or as two Myprocam® 15 mg capsules, taken once daily.42-43

Side effects include dizziness and drowsiness. Other anticholinergic effects such as dry mouth, blurred vision, constipation and urinary retention will be expected due to activity on cholinergic receptors. Cardiac arrhythmias like QTc prolongation is likely to arise and should be used with caution in patients with a history of arrhythmias or who are using any medications prolonging the QTc interval. Myprocam is contra-indicated in patients older than 65 years, or in patients with impaired liver function.41-43

Adequate evidence for the effectiveness of the prolonged use of Myprocam* is not available and therapy for longer periods of use...
is seldom warranted, the duration of use should hence only be for short periods of not more than three weeks.41–43

Conclusion
Muscle pain, or myalgia can be in one targeted area or across many muscles. The severity of muscle pain can range from mild to severe depending on the cause. It usually occurs with overuse of the muscles, inflammation or trauma causing excitation of muscle nociceptor but is also frequently associated with a viral infection. The effective management of patients with muscle pain is through a step-wise approach, offering the greatest potential for maximum analgesia and the minimum adverse effects. Non-pharmacological and pharmacological management are often applied for patients with chronic or recurrent muscle pain associated with medical disease or injury. Pharmacological management, depending on the severity of muscle pain, may include OTC medicines such as aspirin, ibuprofen and/or paracetamol or prescription medicine such as other NSAIDs (diclofenac, naproxen, mefenamic acid, etc) or opioids for moderate to severe muscle pain. Adjunctive therapy is sometimes necessary to manage the side-effects of medications, provide symptom relief, treat anxiety or to manage related or underlying conditions.

References