Pain is a common feature of most rheumatic diseases and it is often the main reason for the patient to seek for a clinical appointment. Chronic pain has a major impact on patient’s quality of life, being frequently associated with functional incapacity, sleep and mood disorders. This leads to absenteeism and heavy consumption of health resources, both representing huge burdens on national economy.

Managing musculoskeletal pain is pivotal but can be challenging. The use of the available pharmaceutical armamentarium should be parsimonious. Opioids are strong analgesic drugs that mostly act through their agonist action on μ-receptors in the central nervous system. Opioid-related side effects are not negligible and are mediated through both central and peripheral opioid receptors. The use of opioids is well established in the treatment of oncologic pain but their role in the management of musculoskeletal pain is still controversial.

Inflammatory rheumatic diseases, osteoarthritis, osteoporotic fractures, chronic low back pain and fibromyalgia represent diverse major rheumatic conditions that frequently lead to chronic pain. In order to standardize and optimize management of musculoskeletal chronic pain in these prevalent diseases, the Portuguese Rheumatology Society elaborated this position paper. The objectives were: a) to define the importance of pain assessment and classification; b) to guide patient selection, appropriate choice of opioids, their management, and raise awareness of their adverse effects; c) to review the existent data on possible indications of opioid therapy on rheumatic diseases.

**Keywords:** Opioids; Musculoskeletal pain; Pain; Rheumatic diseases.

**INTRODUCTION**

Chronic pain is a widespread problem that affects the patient in a multidimensional way. Besides being associated with functional incapacity, sleep and mood disorders, it has also a huge burden on national economy. According to Portuguese Directorate-General of Health (DGS), chronic pain is defined as pain lasting longer than three months or beyond the expected period of healing. Azevedo LF et al. reported that more than one third of the Portuguese population suffers from chronic pain. Musculoskeletal pain was the main cause of chronic pain in this study, with osteoarthritis (OA) being responsible for 42% of the cases.

Managing musculoskeletal pain can be challenging. It requires a multimodal treatment plan considering individuals’ dimension of pain, which goes beyond the prescription of analgesics. It includes planning diagnostic strategies, setting up a treatment plan, getting patients adherence and maintaining a regular follow-up to assess adverse events and achievement of treatment goals.

In 1986, Word Health Organization (WHO) developed a model for the introduction and titration of analgesics in cancer pain relief, known as WHO analgesic ladder. Even though the application of this stepladder...
approach was initially intended for oncologic pain, it has been extrapolated for chronic non-cancer pain (CNCP), raising controversy.4

Paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly considered first-line drugs in treating musculoskeletal pain. NSAIDs are effective in treating inflammatory pain and are a useful weapon in chronic recurrent pain. Chronic use of NSAIDs may be associated with adverse effects related to their renal, gastric and cardiac toxicity, especially in the elderly. Thus, opioid analgesics might emerge as an alternative.

Opioids are strong analgesic drugs. They act on three classical types of opioid receptors - μ, δ, κ - as agonist, antagonists or partial agonists. Their analgesic effect result mainly from their agonist action on μ receptors in the central nervous system (CNS), and side effects are mediated through both central and peripheral opioid receptors.7,8 Due to inter-individual variability in responsiveness to different opioids, the choice of appropriate opioids should be individualized.1

Although the use of opioids in oncologic pain is well established, their role in CNCP is still controversial.9,10 CNCP conditions encompass a variety of conditions with diverse pathogenic mechanisms, including musculoskeletal disorders but also other non-musculoskeletal conditions (e.g., trigeminal neuralgia, headache, etc.). Therefore, defining candidates for opioid treatment is a challenging task that must weigh the risk benefit ratio, including: (i) a wide range of adverse effects, especially in the elderly; (ii) important pharmacologic interactions with commonly used drugs in chronic pain (antidepressants, anticonvulsants, hypnotics, etc.); and also (iii) adverse outcomes associated with addiction and abuse. The opioid crisis has been a growing problem. In 2017, more than 70,200 Americans died from drug overdose, of these, 17,029 were related to opioids.11

The efficacy of opioids for CNCP has been demonstrated in short-term trials.12 However, knowledge on long-term use efficacy and safety is lacking, raising important concerns on their chronic use, provided that many of these CNCP conditions are associated with long life expectancy.10

By this means, an international concern regarding the inadequate widespread use of opioids to treat CNCP disorders and new recommendations to manage non-malignant pain are emerging.9,10,12,13

In order to standardize and optimize management of musculoskeletal chronic pain, Portuguese Rheumatology Society elaborated a position paper with the following goals:

- To define the importance of pain assessment and classification;
- To guide patient selection, appropriate choice of opioids, their management, and raise awareness of their adverse effects;
- To review the existent data on possible indications of opioid therapy on the following situations:
  - Osteoarthritis
  - Chronic low back pain
  - Osteoporotic fractures
  - Fibromyalgia
  - Inflammatory rheumatic diseases

METHODS

We performed a comprehensive search for recommendations of national and international societies, systematic literature reviews (SLR), meta-analysis, and original articles from 2000 until May 2019, using Medline and Cochrane databases.

Our search focused on two major questions: A) Which are the general principles of opioids use, and B) Which are their possible indications in musculoskeletal diseases. Regarding the first question, we search for articles focusing on pain pathophysiology and patient approach, international guidelines on opioids initiation and titration, and summary of products characteristics (SmPC). Concerning the second question, the including criteria were articles addressing the use and efficacy of opioids in adult patients with OA, low back pain (LBP), osteoporotic fractures, fibromyalgia, and inflammatory rheumatic diseases. The exclusion criteria were inadequate population, and deviation from the theme.

The present document was initially presented and discussed on a Pain Work Group of the Portuguese Rheumatology Society meeting in May 2019, and finally sent to all Portuguese rheumatologists for further revisions. This position paper in not regarded as guideline with evidence levels or a systematic review in a strict sense but represents the first Portuguese comprehensive search in the field in order to improve the management of chronic musculoskeletal pain.

GENERAL PRINCIPLES REGARDING OPIOID USE

PAIN ASSESSMENT AND CLASSIFICATION
According to International Association for the Study of Pain (IASP), pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”, representing a multidimensional phenomenon with impact mainly in four scopes: physical, mental, social, and professional. It can be classified according to its duration, location, and referral, pathogenesis (nociceptive, neuropathic, nociplastic), irradiation, intensity, associated symptoms, etc. Rheumatic conditions are often divided into three broad categories based on underlying pathogenesis and presumed etiology of pain: inflammatory (e.g. RA), mechanic or degenerative (e.g. OA) and nociplastic (e.g. fibromyalgia).

All patients undergoing medical assessment should be screened for pain, using visual analogue scale (VAS) or numeric pain intensity scale (NPIIS). Distinction between nociceptive mechanic and nociceptive inflammatory pain has therapeutic impact, since it might help to decide whether to use analgesics or NSAIDs drugs. Characterizing pain in conjunction with physical examination and complementary studies provide important clues about etiologic diagnosis which is of utmost importance to provide target-based therapy.

Physicians should also assess functional capacity, impact on daily activities and absenteeism rate, significant co-morbidities mental health, and quality of sleep. Azevedo LF et al. demonstrated that 35% of individuals with chronic pain also reported moderate-to-severe disability affecting professional and family activities and ability to sleep, and 13% reported concomitant diagnosis of depression/anxiety disorder. Therefore, as part of an approach to chronic pain in all its dimensions, preventing mental illness is a crucial need.

When pain control is not obtained with optimized treatment, physicians should search for an alternative diagnosis before escalating analgesic treatment; in this setting, a multidisciplinary approach might be reasonable. Notwithstanding, before defining a therapeutic plan it is important to establish therapeutic goals, approaching patients’ expectations. Having an utopic goal of becoming pain-free can lead to frustration and excessive dose adjustments.

**PATIENT SELECTION, OPIOID SELECTION AND SPECIAL PRECAUTIONS**

Proper selection of candidates for opioid treatment might be the most important and challenging task. Even though, it might be tempting to use opioids simply based on a report of moderate to severe pain, recent evidence actually restricts its use when all alternative treatments have failed. On the other hand, in some conditions, opioids may even hinder recovery. In fact, opioid numbing effect might interfere with physical exercise capacity, which in some cases, such as fibromyalgia and LBP, is the intervention most likely to achieve improvement. Decisions about the suitability for opioid treatment must be made on an individual patient basis. Screening for personal history of substance abuse and psychiatric disorder is also important since it can be associated with a higher risk of opioid abuse/addiction.

Once opioid-based therapy is chosen, patients should start with low dose and up-titrator stepwise, monitoring efficacy and adverse events on a monthly basis or even more frequently if necessary. The choice of the opioid should be individualized, regarding that no single opioid is superior to another. Physician should take into consideration three main factors: age, comorbidities (renal and/or hepatic insufficiency), and possible drug interactions. Either long-acting opioid (LAO) or short-acting opioid (SAO) can be used. However, especially for opioid-naive patients, a low-dose SAO is often favored for the initial opioid therapy since it can be titrated more rapidly and safely than LAOs. Response to opioid trial is also informative of future efficacy. Some formulations are not appropriate for treatment initiation, such as transdermal fentanyl patches - which can cause severe respiratory depression in opioid-naive patients - and methadone - due to its unpredictable pharmacokinetics.

Dose titration should be stepwise; in general, dose increases of 30-50% are recommended. After stable maintenance for 8 to 12 weeks with appropriate outcomes, it is essential to decide to either continue or discontinue the therapy. In the presence of any indication of abuse, misuse, aberrant behavior or important adverse effects, the physician must taper the drug therapy and discontinue. Tapering may be carried out slowly with a decrease by 10% of the original dose per week. Opioid therapy beyond 12 weeks lacks strong evidence to support its use regarding efficacy and safety.

When the patient fails to achieve therapeutic goals, switching to another opioid may be indicated. For this matter, the equianalgesic dose should be determined using a published equivalence table and the new opioid starting dose should be 25-50% lower than the calculated dose. However, the physician should...
first search for other causes that may sustain the uncontrolled pain, namely (i) “is the baseline diseased controlled?” and (ii) “is there any missing diagnosis?”.

Such questioning is of the utmost importance because the patient might need targeted therapy, instead of analgesic treatment on its own.

Regarding some special situations, additional precautions are needed. If renal dysfunction is present, usually codeine, tramadol and morphine are not the best option, since renal adjustment is needed. Tramadol, tapentadol, morphine, hydromorphone, and oxycodone doses should also be reduced in patients with hepatic impairment. Generally, the use of buprenorphine patches is safe in the elderly population, due to its low drug-interaction profile, lack of need for renal/hepatic dose adjustment and lesser risk of respiratory depression

Table I summarizes opioid formulation, posology and maximum daily doses.

**DRUGS AND DOSAGE**

Table III summarizes opioid formulation, posology and maximum daily doses.

**ADVERSE EFFECTS**

Medication regimens should be individualized. These drugs should only be used when they are expected to be effective.

Common opioid adverse effects, which are dose and time dependent, include gastrointestinal disturbance such as constipation, nausea, and vomiting. Constipation is frequent, and laxatives along with oral hydration and dietary measures are the first intervention indicated. If nausea and vomiting are frequent, antiemetics are recommended.

Other adverse events include fatigue, CNS effects (dizziness, confusion, sedation, euphoria, dysphoria, and restlessness), genitourinary effects (urinary retention), cholinergic effects (xerostomia, bradycardia),...
pruritus, etc.
Although not common, respiratory depression is a serious and potentially life-threatening side effect. This risk is increased in the setting of underlying pulmonary disease or when combined with sedatives.

With chronic administration of opioids, tolerance and physical dependence may occur. Tolerance may lead to the need for higher doses to achieve the same level of pain control. Physical dependence results in withdrawal symptoms if an opioid is abruptly discontinued or a patient receives an opioid antagonist. Withdrawal symptoms include restlessness, rhinorrhea, sneezing, sweating, insomnia, tremor, gastrointestinal symptoms, fever, hypertension, tachycardia and tachypnea, etc.

Due to opioid effects on mood and reward behaviors, some patients may misuse or abuse them.

Although most adverse effects are minor and resolve with continued use, some are long-lasting, serious, or may increase with the ongoing use. Therefore, proper monitoring and regular follow-up is crucial.

POSSIBLE INDICATIONS IN MUSCULOSKELETAL DISEASES

OSTEOARTHRITIS

OA is by far the most prevalent joint disease and a leading cause of disability in older adults. In Portugal, the estimated prevalence of knee OA, hand OA and hip OA is 12.4%, 8.7% and 2.9%, respectively.

When patients experience OA flares, joint effusion is common, as in classical inflammatory arthropathies; in these circumstances they are better treated with NSAIDs.

International recommendations for management of OA are divided into three main categories: non-pharmacological, pharmacological, and surgical.

In American College of Rheumatology (ACR) recommendations for the treatment of hand, hip and knee OA, tramadol was considered separately from opioid analgesics because its central analgesic effect is thought to be mediated not only by a weak opioid receptor agonist effect but also through modulation of serotonin and norepinephrine levels. Opioid analgesics are recommended only for patients with symptomatic OA with an inadequate response to both non-pharmacologic and pharmacologic modalities (eg. paracetamol, NSAIDs, intraarticular corticosteroid injections, chondroitin sulfate, glucosamine, topical capsaicin) and who are either unwilling to undergo or are not candidates for total joint arthroplasty.

In hip OA, according to European League Against Rheumatism (EULAR) recommendations, opioid analgesics are useful alternatives in patients in whom NSAIDs are contraindicated, ineffective, and/or poorly tolerated. One systematic review reported that a single dose of a combination of paracetamol and codeine increases by about 5% the analgesic strength of treatment of any type of pain, including pain due to hip OA. Although the combination of paracetamol and opioid provided better analgesia than placebo, this treatment...
<table>
<thead>
<tr>
<th>Active substance</th>
<th>Formulation</th>
<th>Posology</th>
<th>Final dose maximum daily dose</th>
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<tbody>
<tr>
<td><strong>Weak opioids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Paracetamol +)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td></td>
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<tr>
<td>Tablets: 500 mg + 20 mg; 500mg + 20mg; 1000mg + 60mg; Capsule: 500mg + 30mg Syrup: 40 mg/ml + 1 mg/ml</td>
<td>Up to 3 times a day</td>
<td>Paracetamol: 4g; Codeine: 240 mg</td>
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</tr>
<tr>
<td>Tapentadol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tablets: 50mg; 75mg; 100mg</td>
<td></td>
<td></td>
<td>400mg</td>
</tr>
<tr>
<td>Prolonged-release tablets: 25mg; 50; 100mg; 150mg; 200mg; 250mg; Oral solution: 4 mg/ml; 20mg/ml</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Strong opioids</strong></td>
<td></td>
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<tr>
<td>Buprenorphine</td>
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<tr>
<td>Sublingual tablets: 0.4mg; 2mg; 8mg; Transdermal patch: 35 µg/h; 52.5 µg/h; 70 µg/h</td>
<td></td>
<td>Transdermal patch: 70 µg/h every 72h Sublingual tablets: 16 mg</td>
<td></td>
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<tr>
<td>Oxycodone</td>
<td></td>
<td></td>
<td>400 mg</td>
</tr>
<tr>
<td>Prolonged-release tablets: 5mg; 10mg; 15mg; 20mg; 30mg; 40mg; 80mg</td>
<td>Patients never receiving opioids: 10 mg 12/12h.</td>
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<tr>
<td>Fentanyl</td>
<td></td>
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<tr>
<td>Sublingual tablets: 30 µg; 50 µg; 67 µg; 100µg; 133 µg; 200µg; 267 µg; 300µg; 400µg; 533 µg; 600 µg; 800 µg Transdermal patch: 12 µg/h; 12.5 µg/h; 25 µg/h; 50 µg/h; 75 µg/h; 100 µg/h Injectable solution: 1 mg/2 ml; 25 mg/50 ml; 5 mg/10 ml; 0.05 mg/ml Powder for solution for infusion or infusion: 1mg; 2mg; 5mg</td>
<td>Sublingual tablets: only for disruptive pain. Start treatment with a single sublingual tablet of 100 micrograms, sublingual tablet of 100 micrograms. It should not be taken at intervals of less than 2 hours, nor more than 4 times a day. It is recommended that fentanyl patch be used by patients who have demonstrated tolerance to opioids. Transdermal patch: replaced every 72 hours. Injectable solution: only used in hospital</td>
<td>Sublingual tablets: 800 µg Transdermal patch: 100 µg/h every 72h</td>
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<tr>
<td>Hydromorphone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged-release tablets: 4mg; 8mg; 16mg; 32mg; 64mg</td>
<td>Patients not receiving opioids: the dose should be 8 mg. Some may benefit from an initial titration dose of 4 mg.</td>
<td>64 mg</td>
<td></td>
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<tr>
<td>Morphine</td>
<td></td>
<td></td>
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<tr>
<td>Prolonged-release tablets: 10mg; 30mg; 60mg; 100mg; 200mg; Prolonged-release capsules: 10mg; 20mg; 30mg; 40mg; 50mg; 60mg; 90mg; 100mg; 120mg; 150mg; 200mg; Modified release tablets/capsules: 10mg; 30mg; 60mg; 100mg Sublingual tablets: 2mg; 3mg; Oral solution: 2 mg/ml; 6 mg/ml; 20 mg/ml Injectable solution: 5 mg/1 ml; 10 mg/1 ml; 20 mg/2 ml; 20 mg/1 ml; 40 mg/2 ml</td>
<td>Tablets/oral solutions: 10 mg morphine sulfate every 4 hours Prolonged capsules/tablets: start treatment with one or two 10 mg tablets 12/12h. Morphine may be administered subcutaneously, intramuscularly and intravenously, in hospital used.</td>
<td>Not applicable</td>
<td></td>
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h: hours; mg: milligrams; ml: milliliters; ug: microgram
was no better than paracetamol and was inferior to diclofenac^37.

EULAR recommendations for knee OA are similar to those regarding hip OA. A randomized clinical trial (RCT) of 90 patients showed that tramadol allowed reduction of the naproxen dose among those patients with naproxen-responsive pain^48. An RCT regarding opioid treatment vs non-opioid treatment (SPACE) showed no significant differences in pain-related function over 12 months in either hip or knee OA. In fact, pain intensity was significantly lower in the non-opioid group and adverse medication-related symptoms were significantly more common in the opioid group over 12 months. Noteworthy, this study considers tramadol therapy in the non-opioid group^39.

In hand OA, oral analgesics, particularly NSAIDs, should be considered for a limited duration for relief of symptoms. Oral NSAIDs effectively improved pain and function. The efficacy of paracetamol in hand OA is still uncertain, so it is reserved when oral NSAIDs are contraindicated^38. Tramadol was also regarded by the task force as an alternative oral analgesic although currently there is no evidence to support its use^50.

Tapentadol significantly reduced average pain intensity from baseline to week 12 in a placebo control study of patients with moderate-to-severe chronic pain associated with OA^31. Further studies are needed to assess its long-term efficacy and safety.

A recent meta-analysis including 8 trials with tramadol, 6 with oxycodeone, 2 with tapentadol, 2 with hydromorphone and 1 with hydrocodone, reported significantly more adverse effects affecting the lower and upper GI tract, skin and CNS with all opioid formulations versus placebo. This emphasizes the concept that there are considerable safety and tolerability issues concerning the use of opioids in OA and its use should only be considered after failure of other analgesic options and for short periods of time^52.

**CHRONIC LOW BACK PAIN**

LBP is a common condition seen in clinical practice and the leading cause of disability worldwide^35. In Portugal, the estimated prevalence of LBP is estimated in 26.4%^41.

A systematic review^54 supported the use of paracetamol and NSAIDs as first line pharmacologic options for LBP. Secondary options were muscle relaxants, benzodiazepines and antidepressants. However, when these are ineffective or contraindicated, opioid analgesics may be beneficial alternatives^55.

European guidelines recommended the use of weak opioids in patients with nonspecific chronic LBP who do not respond to other treatment modalities^56. In fact, the combination therapy of tramadol-paracetamol appeared to be effective in chronic LBP^57. Although these seem to have an effect on pain, the benefits on function are less clear^48. The evidence for the use of strong opioids in LBP is limited. One systematic review^58 found that strong opioids were associated with greater short-term pain relief than placebo for pain. Given the short duration of available studies, the effectiveness and safety of long-term opioid treatment for chronic LBP remains unproven^59.

**OSTEOPOROTIC FRACTURES**

Osteoporosis is characterized by an increased risk of fractures, related to decreased bone mass and microstructural alterations of the bone. Pain is common and up to 85% of osteoporotic patients suffer from acute or chronic pain^61.

In the event of an osteoporotic fracture, the immediate goals of treatment are pain control and fracture stability. An osteoporotic fracture often starts a vicious circle of pain, immobility, muscle atrophy, which should be cut shortly by an effective long-term strategy based on an aggressive and efficient multimodal pain management and functional rehabilitation^62.

Anti-osteoporotic drugs can partially control pain and should always be the cornerstone of osteoporotic pain treatment. The analgesic effect of anti-osteoporotic treatment in bone pain has already been confirmed in several clinical trials, and is probably the result of their action on bone turnover, mainly in reabsorption^63–73.

Non-pharmacological treatment must not be forgotten, and orthotics, exercise and rehabilitation, among other measures, may be considered for pain control. Nevertheless, additional analgesics are most likely necessary for pain relief, at least in the acute and subacute phase of fractures. Opioids may be inevitable to successfully control pain and prevent the risk of evolving to a chronic pain state. In the specific case of vertebral fractures, vertebral augmentation (percutaneous vertebroplasty or kyphoplasty) may represent a valid therapeutic option, reducing the need for higher dose of analgesics, including opioids^54.

Opioid treatment controls the whole spectrum of pain pathogenic mechanisms in acute and chronic osteoporotic pain, but opioid drugs have different profiles...
concerning their efficacy on neuropathic components, tolerability, and safety.

Taptental is a centrally active analgesic drug with μ-opioid-receptor agonist and noradrenalin re-uptake inhibitor activity, making it effective in acute and chronic pain in osteoporosis.\textsuperscript{75–77}

Notwithstanding, there are specific risks concerning the use of opioids in osteoporosis. The risk of opioid induced fractures remains unclear but there are significant differences in the relative fracture risk among different opioids. Opioids significantly reduce osteoblast activity by reducing osteocalcin levels.\textsuperscript{78,79} This osteoporotic risk results both from direct and indirect interference with complex mechanisms that control bone turnover, as well as from hormonal changes that may also lead to hypogonadism, sexual dysfunction, decreased muscle mass, fatigue and depression.

Falls are a major risk factor for osteoporotic fracture and constitute another important aspect concerning opioid treatment risks in osteoporosis. There is a strong association between these CNS acting drugs with falls, particularly in the elderly population.\textsuperscript{75,80}

Despite the absence of evidence concerning the efficacy of gabapentinoids and antidepressants (especially SNRIs) in osteoporotic pain treatment, its demonstrated effect on neuropathic pain supports their occasional use with good results in osteoporotic pain, and some authors suggest a potential opioid-sparing effect.\textsuperscript{81–85} Nevertheless, their use for pain in osteoporosis remains controversial, as both drugs may also be implicated in bone mineral density reduction, increased risk of falls and increased risk of fractures.\textsuperscript{82,84}

**FIBROMYALGIA**

Fibromyalgia is a common disease affecting 2.0% of the general population\textsuperscript{86} and about 1.7% of the Portuguese population (3.1% in women, and 0.1% in men).\textsuperscript{91}

Management of fibromyalgia should aim at improving health-related quality of life, carefully weighing the benefits and risks of treatment, while engaging patients as active participants in the process. It often requires a combination of non-pharmacological and pharmacological treatment modalities tailored according to pain intensity, function and associated features. Non-pharmacological treatment, including education, cognitive behavioral therapy and exercise is the cornerstone of the therapeutic plan, with proved efficacy in fibromyalgia.\textsuperscript{87} Adherence and compliance to treatment are, however, important limitations when trying to complement these non-pharmacological approaches. Pharmacological treatment options include amitriptyline, duloxetine, milnacipran, pregabalin, cyclobenzaprine or tramadol, which should be considered in people with severe pain.\textsuperscript{88}

Bennett et al. presented the only study comparing the combination of tramadol with paracetamol to placebo treatment in a 13 week, parallel design trial (315 participants). Patients in the combination therapy group (65/156) reported significantly more pain relief (≥ 30%) in comparison with the placebo group (37/157). Quality of evidence was considered very low because of the limited number of responders. Significantly more participants taking placebo discontinued due to lack of efficacy and significantly more participants in the combination group reported at least one adverse event.\textsuperscript{88,89}

A recent trial with 971 patients evaluating the efficacy of brief interdisciplinary fibromyalgia treatment program showed that opioid users had worse symptom severity (using the Fibromyalgia Impact Questionnaire) as well as worse quality of life (using the Short Form-36 Health Status Questionnaire) at baseline and post treatment, with significantly less improvement in the opioid users compared with the non-opioid users.\textsuperscript{90} The hyperactive endogenous opioid system in fibromyalgia may also explain why opioids not only appear to be ineffective, but also might worsen fibromyalgia-related hyperalgesia.\textsuperscript{87} On the other hand, opioid-induced sedation might interfere with adherence to non-pharmacologic therapy, such as physical exercise.\textsuperscript{17} The literature research did not identify benefit of strong opioids on fibromyalgia.\textsuperscript{91}

**INFLAMMATORY RHEUMATIC DISEASES**

The last decades have witnessed considerable advances in the management of inflammatory arthritis, particularly (RA); however, musculoskeletal pain remains an important issue for patients.\textsuperscript{92}

The use of opioids in inflammatory rheumatic diseases is controversial.\textsuperscript{93}

Opioids have been used restrictively in RA and it is difficult to establish their role on its treatment, regarding that there is limited evidence on their risk benefit profile. At the moment, it is not possible to draw conclusions regarding the use of weak opioids for longer than six weeks, or the role of strong opioids.\textsuperscript{94} No RCTs have examined the efficacy of opioids in RA, but it can be reasonable to use them when other therapies, including paracetamol and NSAIDs, have failed or are not tolerated.
Opioids can be employed for short-term use in cases of secondary OA or as bridging therapy until definitive surgical intervention is achieved. Recently, longer term use of these agents is gaining support in chronic degenerative conditions.

Better evidence and revised recommendations are required to better understand and improve treatment of chronic arthritis-related pain (Table IV).

CONCLUSION

Chronic pain is one of the most prevalent and difficult to manage medical conditions. It represents the cornerstone symptom in rheumatology, having a major impact in all aspects of patients’ quality of life. Assessing pain and identifying the underlying pain features and mechanism is of utmost importance in order to personalize the therapeutic plan. After defining realistic therapeutic goals, managing musculoskeletal pain requires not only a combination of pharmacological and non-pharmacological approaches, but also patient’s and physician’s commitment. It is important to understand patient’s goals and expectations, comorbidities, cognitive and functional status, which will influence pharmacological choices and treatment outcomes.

The use of opioids has increased dramatically over the past decade. In the past few years, there has been a range of scientific publications suggesting that prescribed opioid doses are too high and are prescribed for too long, with increasing risk of drug abuse and overdose. Opioids must be a valid therapeutic choice concerning pain treatment in some specific situations; nevertheless, they must be used with caution. There is currently a lack of evidence supporting its efficacy in chronic musculoskeletal pain. Although there are concerns regarding tolerance, addiction and opioid-induced hyperalgesia its use should be considered on a case-by-case basis. According to international guidelines concerning the management of LBP and OA, strong opioids may be prescribed only in unremitting cases for short-term use, stepping down to weaker opioids or removing altogether if not effective. In RA, no study was longer than 6 weeks and there were too few trials of strong opioids to draw any conclusions regarding their efficacy. In fibromyalgia, there is a proven lack of efficacy, and subsequently international guidelines discourage the use of opioids.

Therefore, it is crucial to educate health care professionals on the benefits and risks of opioids, which should improve quality of prescription and monitoring of opioid therapy.

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