The role of opioid analgesics in rheumatic disorders: a position paper from the Portuguese Rheumatology Society

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ABSTRACT

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.

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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[1]. 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[2]. 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[3].

Managing musculoskeletal pain can be challenging. It requires a multimodal treatment plan considering individual's 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[5]. 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[6]. Thus, opioid analgesics might emerge as an alternative.

Opioids are strong analgesic drugs. They act on three classical types of opioid receptors - μ, σ, κ - as agonist, antagonists or partial agonists[7]. 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[9]. 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 this 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"[14], 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.[15]. 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)[16].

All patients undergoing medical assessment should be screened for pain[1], using visual analogue scale (VAS) or numeric pain intensity scale (NPIS). 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[3]. 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[17]. Even though, it might be tempting to use opioids simply based on a report of moderate to severe pain[18], recent evidence actually restricts its use when all alternative treatments have failed[17]. 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[17]. 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-titrate stepwise, monitoring efficacy and adverse events on a monthly basis or even more frequently if necessary[1,17]. 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[1]. Either long-acting opioid (LAO) or short-acting opioid (SAO) can be used[19,20]. However, especially for opioid-naïve 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[20]. Some formulations are not appropriate for treatment initiation, such as transdermal fentanyl patches - which can cause severe respiratory depression in opioid-naïve patients - and methadone - due to its unpredictable pharmacokinetics[20].

Dose titration should be stepwise; in general, dose increases of 30-50% are recommended[20]. 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[9]. Opioid therapy beyond 12 weeks lacks strong evidence to support its use regarding efficacy and safety[21,22].

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 (Table I) and the new opioid starting dose should be 25-50% lower than the calculated dose [1,23]. However, the physician should

TABLE I. OPIOID EQUIVALENCE TABLE

Equianalgesic Doses																			
Oral																			
Morphine (mg)	10	20	30	40	50	60	70	80	90	100	110	120	130	140	150	160	170	180	200
Tapentadol (mg)		50		100		150		200		250		300		350		400		450	200
Oxycodone (mg)	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90	100
Tramadol (mg)	50	100	150	200	300	350	400												
Codeine (mg)	90	210	330																
Hydromorphone (mg)		4		8		12		16		20		24		28		32		36	40
Injectable																			
Morphine (iv mg)			10			20			30			40			50			60	
Morphine (sc mg)		10		20		30		40		50		60		70		80			100
Tramadol (iv/sc mg)			100			200			300			400							
Transdermal																			
Fentanyl (μg/h)				12.5				25						50					
Buprenorphine (μg/h)								35				52.5				70			

Iv: intravenous; mg: milligrams; sc: subcutaneous; μg/h: microgram/hour

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[1]. Tapentadol might also be an option due to its good pharmacokinetic profile, with low protein binding and distribution volume; yet, it does need renal adjustment (GFR<30 ml/min)[24]. Tramadol should be used with caution in older adults, especially if already taking drugs that interfere with serotonin (e.g., antidepressants), because of the serotoninergic syndrome risk, and the maximum daily dose should be reduced from 400 mg to 300 mg in the elderly.

Opioids can potentiate the effects of other central acting drugs and must be used very cautiously in conjunction with CNS depressants such as alcohol, sedatives, hypnotics, H1-receptor antagonists, barbiturates, antidepressants or antipsychotics.

The use of opioids should be avoided in patients with obstructive sleep apnea syndrome and during pregnancy[25] (Table II).

DRUGS AND DOSAGE

Table III summarizes opioid formulation, posology and maximum daily doses[24,26–36].

ADVERSE EFFECTS

Medication regimens should be individualized. These drugs should only be used when they are expected to be effective[37].

Common opioid adverse effects, which are dose and time dependent[38], 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[39].

Other adverse events include fatigue, CNS effects (dizziness, confusion, sedation, euphoria, dysphoria, and restlessness), genitourinary effects (urinary retention), cholinergic effects (xerostomia, bradycardia),

TABLE II. OPIOID SELECTION HIGHLIGHTS

- Patients should be screened for risk of misuse or addiction and other risk factors for possible complications.
- The choice of the opioid should be individualized.
- No single opioid is superior to another.
- There is no ideal starting dose. Start with the lowest possible dose, and up titrate stepwise.
- Regular follow-up is needed to monitor adverse events and efficacy.
- Short-acting opioids might be a safer option in opioid-naïve patients.
- When switching opioids, establish the equianalgesic dose and reduce the starting dose of the new opioid by a factor of 25-50%.
- Weak opioids: tramadol, codeine, tapentadol.
- Strong opioids: morphine, oxycodone, hydromorphone, buprenorphine, fentanyl.
- Use with caution in patients already taking central acting drugs such as antidepressants, hypnotics, anticonvulsants, etc.
- Association of laxatives and prokinetics drugs may prevent some common adverse events.
- Tapering may be carried out slowly with a decrease by 10% of the original dose per week.

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[13].

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[40]. 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 tachypneia, etc[41].

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[42]. 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[43] care . When patients experience OA flares joint effusion is common, as in classical inflammatory arthropathies; in these circumstances they are better treated with NSAIDs[44].

International recommendations for management of OA are divided into three main categories: non-pharmacological, pharmacological, and surgical[45].

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[46].

In hip OA, according to European League Against Rheumatism (EULAR) recommendations, opioid analgesicsare 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 III. OPIOIDS FORMULATION, POSOLOGY AND MAXIMUM DAILY DOSE

Active substance	Formulation	Posology	Final dose maximum daily dose
Weak opioids			
(Paracetamol +) Codeine[31]	Tablets: 500 mg + 20 mg; 500mg + 20mg; 1000mg + 60mg; Capsule: 500mg+ 30mg Syrup: 40 mg/ml + 1 mg/ml Suppository: 1000 mg + 60 mg	Up to 3 times a day	Paracetamol: 4g; Codeine: 240 mg
Tramadol[29]	Capsule: 50mg; Tablets: 100 mg; Prolonged-release capsule: 50mg; 100mg; 150mg; 200mg; Prolonged-release tablets: 100mg; 150mg; 200mg; Injectable solution: 50mg/ml; 100mg/2ml	Capsules or tablets: 6/6 h or 8/8 h, doses may be repeated at intervals of at least 60 minutes, up to a maximum dose. Prolonged release formulations: Twice daily, maximum 8/8h Injections: attack dose of 100 mg. During the first hour supplementary doses of 50 mg every 10 to 20 minutes, not exceeding the total dose of 250 mg. Subsequently: 50 or 100 mg every 4 to 6 hours.	400mg
Tapentadol[28]	Tablets: 50mg; 75mg; 100mg Prolonged-release tablets: 25mg; 50; 100mg; 150mg; 200mg; 250mg; Oral solution: 4 mg/ml; 20mg/ml	Tablets and oral solution: start with 50 mg every 4 to 6 hours. Prolonged release tablets: start with 50 mg twice daily.	Tablets and oral solutions: 600 mg Tablets prolonged--release: 500mg
Strong opioids			
Buprenorphine[35,36]	Sublingual tablets: 0,4mg; 2mg; 8mg; Transdermal patch: 35 µg/h; 52.5 µg/h; 70 µg/h	Sublingual tablets: Start doses: 0.8 to 4 mg, single daily dose. Transdermal patch: patients who have not received prior strong opioids treatment should start with 35 µg/h patch.	Transdermal patch: 70 µg/h every 72h Sublingual tablets: 16 mg
Oxycodone[37]	Prolonged-release tablets: 5mg; 10mg; 15mg; 20mg; 30mg; 40mg; 80mg	Patients never receiving opioids: 10 mg 12/12h.	400 mg
Fentanile[39,40]	Sublingual tablets: 30 µg; 50µg; 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	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 fentanile patch be used by patients who have demonstrated tolerance to opioids. Transdermal patch: replaced every 72 hours. Injectable solution: only used in hospital	Sublingual tablets: 800 µg Transdermal patch: 100 µg/h every 72h
Hydromorphone[38]	Prolonged-release tablets: 4mg; 8mg; 16mg; 32mg; 64mg	Patients not receiving opioids: the dose should be 8 mg. Some may benefit from an initial titration dose of 4 mg.	64 mg
Morphine[32-34]	Prolonged-release tablets: 10mg; 30mg; 60mg; 100mg; 200mg; Prolonged-release capsules: 10mg; 20mg; 30mg; 40mg; 50mg; 60mg; 90mg; 100mg; 120mg; 150mg; 200mg; Modificated 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	Tablets/oral solutions: 10 mg morphine sulfate every 4 hours Prolongated capsules/tablets: start treatment with one or two 10 mg tablets 12/12h. Morphine may be administered subcutaneously, intramuscularly and intravenously, in hospital used.	Not applicable

h: hours; mg: milligrams; ml: milliliters; ug: microgram

was no better than paracetamol and was inferior to diclofenac[47].

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[49].

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[39]. 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[51]. Further studies are needed to assess its long-term efficacy and safety.

A recent meta-analysis including 8 trials with tramadol, 6 with oxycodone, 2 with tapentadol, 2 with hydromorphone and 1 with hydrocodone, reported significantly more adverse events 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[53]. In Portugal, the estimated prevalence of LBP is estimated in 26.4%[43].

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[58]. The evidence for the use of strong opioids in LBP is limited. One systematic review[59] 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[60].

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[74].

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.

Tapentadol 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[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[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[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[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[82,84].

FIBROMYALGIA

Fibromyalgia is a common disease affecting 2.0% of the general population[86] and about 1.7% of the Portuguese population (3.1% in women, and 0.1% in men)[43].

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[87]. Adherence and compliance to treatment are, however, important limitations when trying to implement these non-pharmacological approaches. Pharmacological treatment options include amitriptyline, duloxetine, milnacipran, pregabalin, cyclobenzaprine or tramadol, which should be considered in people with severe pain[86].

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 [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[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[87]. On the other hand, opioid-induced sedation might interfere with adherence to non-pharmacologic therapy, such as physical exercise[17]. The literature research did not identify benefit of strong opioids on fibromyalgia[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[92].

The use of opioids in inflammatory rheumatic diseases is controversial[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[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

TABLE IV. KEY MESSAGES

• All patients should be screened for pain and its impact on daily activities and functional capacity. Associated comorbidities (depression/anxiety; renal/hepatic impairment; history of abuse/addiction problems) should also be assessed.
• Etiologic diagnosis is of upmost importance to provide target-based treatment.
• Decisions about opioid treatment should always take place after a full anamnesis, physical examination and after achieving and documenting a pain diagnosis.
• Not all patients with pain are suitable candidates for opioid-based therapy.
• There is no strong evidence regarding the use of strong opioids in musculoskeletal disorders.
• Opioid therapy might be used in some specific situations such as OA, LBP and osteoporotic fractures refractory to other therapeutic options, for the shortest period. Opioid efficacy in fibromyalgia and inflammatory rheumatic diseases is limited.
• Chronic opioid treatment beyond 12 weeks caresses further clinical validation.

LBP: low back pain; OA: Osteoarthritis

contraindicated[95].

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[5].

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[3,96]. It represents the cornerstone symptom in rheumatology, having a major impact in all aspects of patients' quality of life[1]. Assessing pain and identifying the underlying pain features and mechanism is of upmost importance in order to personalize the therapeutic plan[17]. 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, co-morbidities, cognitive and functional status, which will influence pharmacological choices and treatment outcomes[1,17].

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[11,22]. 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[10,97]. 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[92]. 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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REFERENCES

1. O'Brien T, Christrup LL, Drewes AM, Fallon MT, Kress HG,

McQuay HJ, et al. European Pain Federation position paper on appropriate opioid use in chronic pain management. Eur J Pain Lond Engl. 2017;21(1):3–19.
2. Direção Geral de Saúde. Programa Nacional para a Prevenção e Controlo da Dor. 2008;(No:11/DSCS/DPCD).
3. Azevedo LF, Costa-Pereira A, Mendonça L, Dias CC, Castro-Lopes JM. Epidemiology of Chronic Pain: A Population-Based Nationwide Study on Its Prevalence, Characteristics and Associated Disability in Portugal. J Pain. 2012 Aug 1;13(8):773–783.
4. WHO analgesic ladder: a good concept gone astray | The BMJ [Internet]. [cited 2019 Sep 22]. Available from: https://www.bmj.com/content/352/bmj.i20.full
5. Tehrani M, Aguiar M, Katz JD. Narcotics in Rheumatology. Health Serv Insights. 2013 Jan 1;6:HSI.S10461.
6. Rostom A, Moayyedi P, Hunt R, Canadian Association of Gastroenterology Consensus Group. Canadian consensus guidelines on long-term nonsteroidal anti-inflammatory drug therapy and the need for gastroprotection: benefits versus risks. Aliment Pharmacol Ther. 2009 Mar 1;29(5):481–496.
7. Drewes AM, Jensen RD, Nielsen LM, Droney J, Christrup LL, Arendt-Nielsen L, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. Br J Clin Pharmacol. 2013 Jan;75(1):60–78.
8. Goodman & Gilman's the pharmacological basis of therapeutics - NLM Catalog - NCBI [Internet]. [cited 2019 May 5]. Available from: https://www.ncbi.nlm.nih.gov/nlmcatalog/101708739
9. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. J Pain. 2009 Feb;10(2):113-130.e22.
10. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long term opioid management for chronic noncancer pain. Cochrane Database Syst Rev [Internet]. 2010 [cited 2019 May 19]; Available from: https://www.readcube.com/ articles/10.1002/14651858.CD006605.pub2
11. National Institute on Druga Abuse. Overdose Death Rates [Internet]. 2019 [cited 2019 Oct 2]. Available from: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates
12. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ Can Med Assoc J J Assoc Medicale Can. 2006 May 23;174(11):1589–1594.
13. Manchikanti L, Kaye AM, Knezevic NN, McAnally H, Slavin K, Trescot AM, et al. Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. 2017;20(2S):S3–92.
14. Pain terms: a list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. Pain. 1979 Jun;6(3):249.
15. Woolf CJ, American College of Physicians, American Physiological Society. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med. 2004 Mar 16;140(6):441–451.
16. Borenstein DG, Hassett AL, Pisetsky D. Pain management in rheumatology research, training, and practice. Clin Exp Rheumatol. 2017 Oct;35 Suppl 107(5):2–7.
17. Ballantyne JC. Opioid Therapy in Chronic Pain. Phys Med Rehabil Clin N Am. 2015 May;26(2):201–218.
18. World Health Organization, editor. Cancer pain relief. Geneva : Albany, NY: World Health Organization ; WHO Publications Center USA [distributor]; 1986. 74 p.
19. Ghodke A, Barquero S, Chelminski PR, Ives TJ. Short-Acting Opioids Are Associated with Comparable Analgesia to Long-Acting Opioids in Patients with Chronic Osteoarthritis with a Reduced Opioid Equivalence Dosing. Pain Med. 2018 Nov 1;19(11):2191–2195.
20. Fine PG, Mahajan G, McPherson ML. Long-Acting Opioids and Short-Acting Opioids: Appropriate Use in Chronic Pain Management. Pain Med. 2009 Jul 1;10(suppl_2):S79–88.
21. Franklin GM. Opioids for chronic noncancer pain: A position paper of the American Academy of Neurology. Neurology. 2014 Sep 30;83(14):1277–1284.
22. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Prescription of Long-Acting Opioids and Mortality in Patients With Chronic Noncancer Pain. JAMA. 2016 Jun 14;315(22):2415–2423.
23. Fine PG, Portenoy RK. Establishing "Best Practices" for Opioid Rotation: Conclusions of an Expert Panel. J Pain Symptom Manage. 2009 Sep;38(3):418–425.
24. SmPC de Palexia, last update 13-12-2018.
25. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. JAMA. 2016 Apr 19;315(15):1624–1645.
26. SmPC do Tramal, last update 11-01-2019.
27. SmPC do Dol-U-Ron, last update 23-05-2016.
28. SmPC do Sevredol, last update 10-11-2014.
29. SmPC do Zomorph, last update 09-05-2014.
30. SmPC do Apo-go, last update 06-01-2018.
31. SmPC do Subutex, last update 17-11-2010.
32. SmPC do Transtec, last update 26-08-2009.
33. SmPC do Olbete, last update 22-04-2014.
34. SmPC do Jurnista, last update 08-05-2015.
35. SmPC do Abstral, last update 16-07-2015.
36. SmPC do Durogesic, last update 09-12-2016.
37. Carter GT, Duong V, Ho S, Ngo KC, Greer CL, Weeks DL. Side effects of commonly prescribed analgesic medications. Phys Med Rehabil Clin N Am. 2014 May;25(2):457–470.
38. Tornero-Molina J, Vidal-Fuentes J, Alonso-Ruiz A, Acebes-Cachafeiro C, Arboleya-Rodríguez L, Calvo-Alen J, et al. Documento de consenso de la Sociedad Española de Reumatología para el uso de opioides en el tratamiento del dolor reumático. Reumatol Clínica Engl Ed. 2006 Mar 1;2:S50–54.
39. Argoff CE, Brennan MJ, Camilleri M, Davies A, Fudin J, Galluzzi KE, et al. Consensus Recommendations on Initiating Prescription Therapies for Opioid-Induced Constipation. Pain Med Malden Mass. 2015 Dec;16(12):2324–2337.

40. Volkow ND, McLellan AT. Opioid Abuse in Chronic Pain--Misconceptions and Mitigation Strategies. N Engl J Med. 2016 Mar 31;374(13):1253–1263.
41. Schuckit MA. Treatment of Opioid-Use Disorders. N Engl J Med. 2016 Jul 28;375(4):357–368.
42. Nafziger AN, Barkin RL. Opioid Therapy in Acute and Chronic Pain. J Clin Pharmacol. 2018 Sep;58(9):1111–1122.
43. Branco JC. EpiReumaPt Reuma Census: A unique and indispensable project. Portuguese Epidemiologic Study of the Rheumatic Diseases. Sociedade Portuguesa Reumatologia Progress Report Sep'11 to March'13.
44. Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013 Jan;21(1):16–21.
45. Fernandes L, Hagen KB, Bijlsma JWJ, Andreassen O, Christensen P, Conaghan PG, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. Ann Rheum Dis. 2013 Jul;72(7):1125–1135.
46. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res. 2012 Apr;64(4):465–474.
47. Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther K-P, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2005 May;64(5):669–681.
48. Jordan KM, Arden NK, Doherty M, Bannwarth B, Bijlsma JWJ, Dieppe P, et al. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2003 Dec;62(12):1145–1155.
49. Krebs EE, Gravely A, Nugent S, Jensen AC, DeRonne B, Goldsmith ES, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. JAMA. 2018 Mar 6;319(9):872–882.
50. Kloppenburg M, Kroon F, Blanco F, Doherty M, S Dziedzic K, Greibrokk E, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis. 2018 Aug 28;78:annrheumdis-2018.
51. Pergolizzi JV, Taylor R, LeQuang JA, Raffa RB, Bisney J. Tapentadol Extended Release in the Treatment of Severe Chronic Low Back Pain and Osteoarthritis Pain. Pain Ther. 2018 Jun;7(1): 37–57.
52. Fuggle N, Curtis E, Shaw S, Spooner L, Bruyère O, Ntani G, et al. Safety of Opioids in Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis. Drugs Aging. 2019 Apr 1;36(1):129–143.
53. Walker BF. The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. J Spinal Disord. 2000 Jun;13(3):205–217.
54. Chou R, Huffman LH, American Pain Society, American College of Physicians. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007 Oct 2;147(7):505–514.
55. Goodwin JLR, Kraemer JJ, Bajwa ZH. The use of opioids in the treatment of osteoarthritis: When, why, and how? Curr Rheumatol Rep. 2009 Feb 1;11(1):5–14.
56. Airaksinen O, Brox JI, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4. European guidelines for the management of chronic nonspecific low back pain. Eur Spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc. 2006 Mar;15 Suppl 2:S192-300.
57. Romanò CL, Romanò D, Lacerenza M. Antineuropathic and antinociceptive drugs combination in patients with chronic low back pain: a systematic review. Pain Res Treat. 2012;2012: 154781.
58. Koes BW, Backes D, Bindels PJE. Pharmacotherapy for chronic non-specific low back pain: current and future options. Expert Opin Pharmacother. 2018;19(6):537–545.
59. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev. 2013 Aug 27;(8):CD004959.
60. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. BMJ. 2015 Jan 5;350:g6380.
61. Hernlund E, Svedbom A, Ivergård M, Compston J, Cooper C, Stenmark J, et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Arch Osteoporos. 2013;8:136.
62. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster J-Y, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2013 Jan;24(1):23–57.
63. Iwamoto J, Makita K, Sato Y, Takeda T, Matsumoto H. Alendronate is more effective than elcatonin in improving pain and quality of life in postmenopausal women with osteoporosis. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2011 Oct;22(10):2735–2742.
64. Ohtori S, Akazawa T, Murata Y, Kinoshita T, Yamashita M, Nakagawa K, et al. Risedronate decreases bone resorption and improves low back pain in postmenopausal osteoporosis patients without vertebral fractures. J Clin Neurosci. 2010 Feb 1;17(2): 209–213.
65. Tetsunaga T, Tetsunaga T, Nishida K, Tanaka M, Sugimoto Y, Takigawa T, et al. Denosumab and alendronate treatment in patients with back pain due to fresh osteoporotic vertebral fractures. J Orthop Sci Off J Jpn Orthop Assoc. 2017 Mar;22(2): 230–236.
66. Petranova T, Sheytanov I, Monov S, Nestorova R, Rashkov R. Denosumab improves bone mineral density and microarchi-

tecture and reduces bone pain in women with osteoporosis with and without glucocorticoid treatment. Biotechnol Biotechnol Equip. 2014 Nov 2;28(6):1127–1137.
67. Scharla S, Oertel H, Helsberg K, Kessler F, Langer F, Nickelsen T. Skeletal pain in postmenopausal women with osteoporosis: prevalence and course during raloxifene treatment in a prospective observational study of 6 months duration. Curr Med Res Opin. 2006 Dec;22(12):2393–2402.
68. Fujita T, Fujii Y, Munezane H, Ohue M, Takagi Y. Analgesic effect of raloxifene on back and knee pain in postmenopausal women with osteoporosis and/or osteoarthritis. J Bone Miner Metab. 2010 Jul 1;28(4):477–484.
69. Sambrook PN, Silverman SL, Cauley JA, Recknor C, Olson M, Su G, et al. Health-related quality of life and treatment of postmenopausal osteoporosis: results from the HORIZON-PFT. Bone. 2011 Jun 1;48(6):1298–1304.
70. Nevitt MC, Chen P, Dore RK, Reginster J-Y, Kiel DP, Zanchetta JR, et al. Reduced risk of back pain following teriparatide treatment: a meta-analysis. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2006 Feb;17(2):273–280.
71. Miller PD, Shergy WJ, Body J-J, Chen P, Rohe ME, Krege JH. Longterm reduction of back pain risk in women with osteoporosis treated with teriparatide compared with alendronate. J Rheumatol. 2005 Aug 1;32(8):1556–1562.
72. Fahrleitner-Pammer A, Langdahl BL, Marin F, Jakob F, Karras D, Barrett A, et al. Fracture rate and back pain during and after discontinuation of teriparatide: 36-month data from the European Forsteo Observational Study (EFOS). Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2011 Oct;22(10):2709–2719.
73. Lyritis G, Marin F, Barker C, Pfeifer M, Farrerons J, Brixen K, et al. Back pain during different sequential treatment regimens of teriparatide: results from EUROFORS. Curr Med Res Opin. 2010 Aug 1;26(8):1799–1807.
74. Francis R, Aspray T, Hide G, M Sutcliffe A, Wilkinson P. Back pain in osteoporotic vertebral fractures. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2008 Aug 1;19:895–903.
75. Vellucci R, Terenzi R, Kanis JA, Kress HG, Mediati RD, Reginster J-Y, et al. Understanding osteoporotic pain and its pharmacological treatment. Osteoporos Int J Establ Result Coop Eur Found Osteoporos Natl Osteoporos Found USA. 2018 Jul;29(7):1477–1491.
76. Kress HG. Tapentadol and its two mechanisms of action: is there a new pharmacological class of centrally-acting analgesics on the horizon? Eur J Pain Lond Engl. 2010 Sep;14(8):781–783.
77. Steigerwald I, Müller M, Davies A, Samper D, Sabatowski R, Baron R, et al. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: results of an open-label, phase 3b study. Curr Med Res Opin. 2012 Jun;28(6):911–936.
78. Pérez-Castrillón JL, Olmos JM, Gómez JJ, Barrallo A, Riancho JA, Perera L, et al. Expression of opioid receptors in osteoblast-like MG-63 cells, and effects of different opioid agonists on alkaline phosphatase and osteocalcin secretion by these cells. Neuroendocrinology. 2000 Sep;72(3):187–194.
79. Coluzzi F, Pergolizzi J, Raffa RB, Mattia C. The unsolved case of "bone-impairing analgesics": the endocrine effects of opioids on bone metabolism. Ther Clin Risk Manag. 2015 Mar 31;11: 515–523.
80. Masud T, Frost M, Ryg J, Matzen L, Ibsen M, Abrahamsen B, et al. Central nervous system medications and falls risk in men aged 60–75 years: the Study on Male Osteoporosis and Aging (SOMA). Age Ageing. 2013 Jan 1;42(1):121–124.
81. Liu B, Liu R, Wang L. A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery. Medicine (Baltimore). 2017 Sep;96(37):e8031.
82. Kanda J, Izumo N, Kobayashi Y, Onodera K, Shimakura T, Yamamoto N, et al. Effects of the Antiepileptic Drugs Phenytoin, Gabapentin, and Levetiracetam on Bone Strength, Bone Mass, and Bone Turnover in Rats. Biol Pharm Bull. 2017;40(11): 1934–1940.
83. Bakken MS, Engeland A, Engesæter LB, Ranhoff AH, Hunskaar S, Ruths S. Increased risk of hip fracture among older people using antidepressant drugs: data from the Norwegian Prescription Database and the Norwegian Hip Fracture Registry. Age Ageing. 2013 Jul;42(4):514–520.
84. Bruyère O, Reginster J-Y. Osteoporosis in patients taking selective serotonin reuptake inhibitors: a focus on fracture outcome. Endocrine. 2015 Feb;48(1):65–68.
85. Lanteigne A, Sheu Y-H, Stürmer T, Pate V, Azrael D, Swanson SA, et al. Serotonin-norepinephrine reuptake inhibitor and selective serotonin reuptake inhibitor use and risk of fractures: a new-user cohort study among US adults aged 50 years and older. CNS Drugs. 2015 Mar;29(3):245–252.
86. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017 Feb;76(2):318–328.
87. Clauw DJ. Fibromyalgia: A Clinical Review. JAMA. 2014 Apr 16;311(15):1547–1555.
88. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. Am J Med. 2003 May;114(7):537–545.
89. Bennett RM, Schein J, Kosinski MR, Hewitt DJ, Jordan DM, Rosenthal NR. Impact of fibromyalgia pain on health-related quality of life before and after treatment with tramadol/acetaminophen. Arthritis Rheum. 2005 Aug 15;53(4):519–527.
90. Hwang J, Lee B, Oh TH, Park D, Kim C. Association between initial opioid use and response to a brief interdisciplinary treatment program in fibromyalgia: Medicine (Baltimore). 2019 Jan;98(1):e13913.
91. Goldenberg DL, Clauw DJ, Palmer RE, Clair AG. Opioid Use in Fibromyalgia: A Cautionary Tale. Mayo Clin Proc. 2016;91(5):640–648.
92. Noori SA, Aiyer R, Yu J, White RS, Mehta N, Gulati A. Nono-

pioid versus opioid agents for chronic neuropathic pain, rheumatoid arthritis pain, cancer pain and low back pain. Pain Manag. 2019 Mar;9(2):205–216.
93. Griessinger N, Sittl R, Jost R, Schaefer M, Likar R. The role of opioid analgesics in rheumatoid disease in the elderly population. Drugs Aging. 2003;20(8):571–583.
94. Whittle SL, Richards BL, Husni E, Buchbinder R. Opioid therapy for treating rheumatoid arthritis pain. Cochrane Database Syst Rev. 2011 Nov 9;(11):CD003113.
95. Whittle SL, Colebatch AN, Buchbinder R, Edwards CJ, Adams K, Englbrecht M, et al. Multinational evidence-based recommendations for pain management by pharmacotherapy in inflammatory arthritis: integrating systematic literature research and expert opinion of a broad panel of rheumatologists in the 3e Initiative. Rheumatol Oxf Engl. 2012 Aug;51(8): 1416–1425.
96. Lidgren L, Smolen J, Bentley G, Delmas P. European Action Towards Better Musculoskeletal Health: A Public Health Strategy to Reduce Burden of Musculoskeletal Conditions. The Bone & Joint Decade. 2005;
97. Eriksen J, Sjøgren P, Bruera E, Ekholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. Pain. 2006 Nov;125(1–2):172–179.