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Latin American reality

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Abstract

**Introduction:** Osteoarthritis is the most common cause of arthritis and one of the principle causes of chronic pain. Although opioids are frequently employed for chronic pain treatment, their usage for osteoarthritis pain remains controversial due to the associated adverse effects. Most guidelines reserve their use for refractory pain in patients with hip and knee osteoarthritis. The situation is even more complex in Latin America, where the prevalence of insufficient pain treatment is high because of the limited availability and use of strong opioids.

**Areas covered:** In this article we review the epidemiology of osteoarthritis, its socioeconomic burden, its impact as a chronic pain cause and the pharmacological treatment options, giving emphasis to the role of strong opioids, their safety and efficacy, especially in Latin American countries, where restrictions regulate their usage.

**Expert commentary:** Usage of strong opioids is safe and effective in the short-term management of osteoarthritis with moderate to severe pain, when other pharmacological treatments are inadequate and surgery is contraindicated, provided their use adheres to existing guidelines. Educational programs for patients and physicians and further research on treating chronic pain with opioids should be implemented to reduce adverse effects and improve care quality.

**Keywords:** Chronic pain, Latin America, osteoarthritis, strong opioids.
Introduction

Osteoarthritis (OA) is the most common form of arthritis and the most prevalent chronic joint disease [1]. Its main anatomopathological features consist of cartilage deterioration in joints, resulting in stiffness, chronic pain and impaired movement. The knees, hands, feet and spine are the joints most commonly affected, followed by the hip and shoulder joints. It is generally accepted by most clinicians that the diagnosis of OA is established late in the disease process, often very late to achieve effective management with currently available therapeutic approaches, thus converting OA into one of the principle causes of chronic pain [1].

While OA is a cause of chronic pain, opioids (especially the strong ones) are not typically prescribed or indicated for the treatment of OA and are reserved until when all other treatment options have been exhausted [2]. In this paper we aspire to provide insight into the arguments for the use of strong opioids in the management of chronic pain caused by OA, and especially their application in the region of Latin America, where the availability and use of opioids is limited and restricted. Opioid treatment can be safe when the guidelines for their use are followed; therefore, their use should be employed only when indicated to improve the quality of life of patients.

This review focuses firstly on the impact of OA as a cause of disability in the general population, emphasizing its effects in the Latinamerican countries. Pain is one of the
most frequent symptom of OA, therefore, the importance of chronic pain and its epidemiology will also be discussed. Lastly, the review will concentrate on the use of major opioids, which are considered to be the most effective of treatments for OA pain, and on those distinctive features, that rule their use in Latinamerica.

1. Prevalence and Impact of OA

OA is the disease most frequently encountered by primary health care physicians and rheumatologists [2,3], it is the single most frequent cause of disability in older adults and its associated costs have a significant impact on the world's health care economy [4,5]. The prevalence of OA is increasing due to population ageing and obesity and estimates published in 2012 suggest that 250 million people are affected by knee OA worldwide [6]. Also genetic factors, sex hormones, racial differences, professional activity, the practice of professional sports, traumas and bone mineral density play an important role [7].

In all the existing OA epidemiological studies the relation between OA and age has been highlighted; however, the underlying mechanism involved is not completely understood. Factors such as biomechanical or biochemical cartilage alterations that cause deterioration of the mechanical properties of the cartilage might be responsible [7]. It has been estimated that the prevalence of OA in persons between 40 and 50 years old is 2,4% for males and 4,4% for females, whereas it can reach up to 25%-40% in persons with 60-65 years of age [8]. Currently the prevalence of OA is estimated to be between 0.5% and 36% in the general population [9]. However,
OA’s prevalence may fluctuate significantly due to the varied clinical features of the disease and the diagnostic criteria used [10].

1.1. Prevalence of OA in Latin America

The prevalence of OA in Latin American countries ranges from 2.3% to 20.4% according to several studies from the Community Oriented program for the Control of Rheumatic Diseases (COPCORD) [11]. However, the prevalence has not been evaluated in all Latin American countries. In 2015 Reginato et al published a descriptive, observational, and cross-sectional study of the demographic and clinical characteristics of OA in Latin America with the participation of 3040 patients from 13 different Latin American countries. The average age of the population involved was 62.5 years with a female-to-male ratio of 4.8:1. Primary OA was the most common form of OA (88%) and the knee (31.2%), the hand (9.5%) and knee and hand combined (22.9%) were the joints most frequently affected by the disease, equally divided between men and women. The incidence of hip OA was estimated to be 1.3%. More than one-third of the patients were obese (38.2%) or hypertensive, almost one-eighth had diabetes and non-steroidal anti-inflammatory drugs (NSAIDs) were used most often to treat the symptoms of OA in all countries [12].

1.2. Impact of OA

Osteoarthritis is a leading cause of disability among older adults [13] and its burden includes chronic pain, which can be either intermittent and severe or persistent background pain [14], with activity limitation and participation restriction [15] and
negative effects on quality of life, mood, fatigue and sleep disturbances [16]. Approximately 80% of OA patients have some degree of movement limitation and 25% have difficulty to perform the activities of the everyday living [17]. The Global Burden of Disease (GBD) Study showed that OA accounted for 0.6% of all disability-adjusted life-years (DALYs = years of life lost + years lived with disability) and also for 2.2% of global years lived with disability [6,18].

It has been suggested that patients with OA have increased mortality [19], however, the effects of OA on quality of life best represent the burden of OA on individuals [17]. It has been reported that the loss in quality-adjusted life years (QALYs) amongst individuals aged 50-84 years due to OA ranges from a mean of 1.9 QALYs to 3.5 QALYs in non-obese and obese patients respectively [20]. Almost 15 million QALYs are lost every year in the USA alone because of OA [17]. These QALYs losses equal those encountered in other highly morbid conditions such as cancer and cardiovascular disease [20].

A very impressive statistic reflects the socioeconomic burden of OA: the cost of OA in the USA, Canada, UK, France and Australia accounts for 1%-2.5% of the gross national product of these countries [21]. This includes the costs of OA that can be directly associated to the disease: hospital stays, elective orthopedic surgery, diagnostic procedures, medications and health professional visits [22,23], which represent in some countries up to 2% of all health-care costs, a proportion similar to the costs of coronary artery disease [24]. However, the majority of the OA costs are
indirect; therefore, the true economic burden of OA is often underestimated [25]. The indirect costs are the consequence of productivity loss due to absenteeism from work or even disease related loss of productivity when the person is at work, premature retirement or death as well as for compensation for household work performed by others (26). With an ageing population, and the prevalence of OA increasing with age, OA is a growing source of indirect costs (27).

2. Epidemiology of chronic pain

As has been mentioned already, the hallmark symptom of OA is chronic pain, causing important disabilities and associated costs. Chronic pain is now recognized as a condition in its own right, corroborated by a certain set of definitions and classifications [28]. In Europe, chronic pain affects almost 20% of the adult population, with the combination of osteoarthritis and rheumatoid arthritis representing the most common cause (42%) of chronic pain: 20% of the patients reported chronic pain due to deteriorated or herniated discs, degeneration or fractures of the spine; 15% had pain from trauma or surgery; migraine and rheumatoid arthritis were involved in less than 10% of the patients; other causes were nerve damage or whiplash, each in 4% of patients [29]. The prevalence of chronic pain varies widely worldwide, with range estimates from 11% to 55% across studies [29] due to differences in the definition of chronic pain, socio-demographic/cultural factors, clinical/psychological factors and survey methodologies. However, the impact of chronic pain is enormous: in the US the annual expenditures related to pain may be higher than those for cancer, heart disease and diabetes combined [30].
2.1. Inadequate pain relief and its consequences

Both in developed and developing countries appropriate treatment for chronic pain patients is not always offered to all of them and a significant percentage of these patients appear to be insufficiently treated [31,32]. Chronic pain patients have the worst quality of life when compared to those with other chronic diseases [33], with feelings of hopelessness/despair and also double the risk of suicide in comparison with people without chronic pain [34,35].

Similarly an important issue, which is not widely explored in OA, is inadequate pain relief (IPR). More specifically there is limited understanding of the relationship between patients and IPR, therapeutic patterns and quality of life (Qol) [36]. Conaghan et al in their study of 1187 patients with knee OA and mean age of 68 years showed that 54% of the study patients met the definition of IPR [36]. Because of variability in treatment effectiveness, tolerability and adherence to treatment, attempts of different treatment modalities are very often required to reduce the prevalence of IPR [37]. Also lack of professional medical attention, failure to use non-pharmacological treating modalities and reliance on monotherapy can also be responsible for IPR [38]. Therefore, treatment for OA should be individualized, taking into account the symptoms of the patient, their preferences and the safety profile of the chosen therapeutic modality [39].
The consequences of IPR are not so clear, as the majority of clinical trials for OA pain relief management focus on the evaluation of pain intensity and treatment response [40,41]. A certain patient profile appears to be at particular risk of IPR: female patients, higher BMI (body mass index), bilateral disease of long duration, cardiovascular disease diabetes and depression [36]. Patients with IPR have more severe pain and physical function loss and consequently lower QoL [37]. It has been suggested that pain forces the patient to reduce their physical activity, resulting in a cycle of pain, inactivity and muscle wasting, which in combination with psychological factors such as anxiety and depression intensify this negative cycle [42]. Quality of life is a complex concept composed of various dimensions such as physical, emotional and social functioning. Many studies (mainly involving patients with knee and hip OA) have shown that OA patients have substantially lower QoL scores in comparison with age-matched norms [43-46]. Despite the overwhelming success of orthopedic procedures, there appears to be a strong correlation between functional outcomes following surgical management of OA and pre-surgical lower QoL, poor emotional health (anxiety/depression), poor coping skills and poor social support [47,48].

2.2. Chronic pain in OA

Pain is a major clinical problem of OA; however, the severity of pain correlates poorly with the structural extent of the joint damage [49]. OA is a disease where the entire joint is involved and both cartilage destruction and soft tissue inflammatory components (synovitis) can be detected [50]. Pro-inflammatory mediators such as nerve growth factor (NGF), nitric oxide (NO) and prostanoids may accumulate in the
OA joint, causing further destruction and pain hypersensitivity (hyperalgesia/allodynia) [51,52]. Currently there is accumulated evidence for the presence of sensitization of pain pathways in OA, with pronounced changes in joint nociceptors and alterations of the nociceptive processing in the spinal cord, brainstem and thalamocortical system [53].

Imaging techniques have provided new information to help comprehend the mechanisms of pain perception in the osteoarthritic joint. MRI is a sensitive technique, the use of which has led to the detection not only of synovitis, but of bone marrow lesions as well, such as necrosis, fibrosis edema and trabecular abnormalities in OA joints [54-57]. Functional Magnetic Resonance Imaging (MRI) and $^{18}$fluorodeoxyglucose (FDG) Positron Emission Tomography scans (PET) have been used in analyzing central pain processing in OA. With these techniques it has been demonstrated that various cortical and thalamic regions of the brain are activated in association with arthritic pain [58,59]. Brain imaging studies may provide a deeper understanding of the treatment processes mechanics, thereby potentiating the development of future analgesic drugs.

3. Opioids for the treatment of chronic pain

Currently opioids are the most commonly used medications in the treatment of chronic pain in accordance with data from the United States, which show that opioids are currently the most popular prescribed drug category: 15% to 20% of the patients seeing a physician are prescribed an opioid and 4 million patients are
prescribed a long-acting opioid every year [60]. In the USA the use of strong opioids for musculoskeletal pain complaints has increased from 2% to 9% between the years of 1980 and 2000. In Australia, the consumption of oral morphine increased five-fold over a period of ten years and in Singapore, 3% of the patients seen in pain clinics were given strong opioids for at least 3 months in a year [61].

However, the use of strong opioids in the treatment of chronic non-cancer pain (CNCP) remains controversial [31, 62]. Manchicanti et al in a recent publication provided an extensive review of the clinical efficacy and safety of the use of opioids in the treatment of CNCP, highlighting the lack of high quality evidence regarding the role of opioids in the management of CNCP [30]. Breivik et al indicated that opioids have a role in selected patients with moderate to severe CNCP, agreeing that there is a limited evidence base for the efficacy and safety of long-term opioid therapy and that additional well-designed studies are required [31, 63, 64]. In 2016 The French Society for the Study and Treatment of Pain published evidenced-based recommendations on the use of strong opioids in chronic non-cancer pain in adults [65]. Following an analysis of 31 cohort studies and 21 meta-analyses, they concluded that strong opioids are not indicated in the treatment of fibromyalgia and primary headaches. Their recommendations regarding strong opioid use were: after failure of first-line treatments, treatment should not last longer than 3 months if no improvement in pain, function or quality of life is observed, doses should not exceed 150mg/day of morphine equivalent, patients should be made aware of the advantages and risks, and risk factors of abuse should be evaluated before prescription and at each renewal.
In Latin America all opioids are considered effective for the treatment of CNCP, but similarly like in the rest of the world there are no well-designed specific studies available. The Change Pain Latin America panel of experts published a study stating that all opioids can be used safely and effectively to treat CNCP and recommended a uniform adoption across the Latin American region [66]. Furthermore, the use of strong opioids for CNCP should be considered when other therapeutic modalities are ineffective for pain relief with cautious monitoring of the patients as their long term use as first-line drugs is still controversial due to the possibility of abuse and dependence [67].

It has been suggested that opioid therapy for CNCP should be in the hands of specialists because of the required knowledge of concepts related to tolerance, chemical dependency, abuse, diversion and monitoring of side effects [68 69], and due to the fact that some physicians’ lack of confidence in prescribing opioids for CNCP for reasons such as opiophobia (fear of abuse and dependency) or opio-ignorance (lack of education and universally accepted consensus guidelines on opioids use, or lack of knowledge and experience in evaluating CNCP adequately) [70,71]. However, this is rather difficult to enforce as access to a pain specialist might be limited, especially in the underdeveloped areas of the globe, and also the large number of patients suffering from OA (with insufficient and delayed treatments) dictates the necessity for the familiarization and involvement of primary care physicians in the management of chronic pain with strong opioids. There is enough evidence suggesting that educational programs can improve opioids prescribers’ confidence [72]. Furthermore, it is important that an exhaustive patient
and pain evaluation is undertaken and use of predetermined outcome measures (reduction in pain scores, improved physical and psychological functioning) are implemented [69].

3.1. The Epidemic of prescription opioid use.

In the last few years, chronic opioid therapy for CNCP has increased to such an extent that the medical use and abuse of opioid analgesic and other controlled substances has reached epidemic proportions in the United States. This has been closely related with an important economic burden and increased complications in many developed countries, including the United States, the United Kingdom, Canada and Australia [73-76]. Increasingly frequent and dramatic reports on the results of overtreatment, misuse, abuse and deaths related to controlled opioids make headline news [77,78]. However, in reality there is probably too much use of opioids for a few patients in a small group of countries and too little use (lack of availability and insufficient prescription) for most other people in the world [79].

In 1961 the United Nations Single Convention on Narcotic Drugs [80] was held in order to ensure the availability of controlled medications for the relief of pain and to prevent diversion and abuse [69]. Nevertheless, as it has been mentioned already, the use of controlled medications remains low in many parts of the world, which is far away from the epidemic extent of opioids use in the United States. Developing countries (including Latin American countries), which represent about 80% of the world’s population, accounted for only about 6% of global strong opioid (e.g.
morphine) consumption [81]. A recent article stated that barriers to the use of opioids include absence of prescriber training, fear of producing opioid dependence, financial constraints, and problems with sourcing or importing opioid medicines, as well as limited availability in pharmacies. Cultural attitudes toward pain management, fear of diversion, and fear of criminal prosecution were also frequent impediments [82].

4. Treating chronic pain with strong opioids in LATAM

Insufficient pain treatment because of limited use of opioids appears to be highly prevalent in Latin America and is directly associated with patient dissatisfaction [66,83]. Latin American countries have more stringent restrictions and laws than those laid down by the International Narcotics Control Board [84], which regulates storage and distribution of opioids. This limits their accessibility and delivery and negatively affects their prescription. Additional limitations for the prescription of opioids come from the lack of knowledge regarding opioid use and their efficacy in the treatment of pain amongst patients and health care professionals (opioid-ignorance) [85,86] and from the fear of possible abuse and addiction (opiophobia). Furthermore, healthcare professionals in some Latin American countries are required to hold a special license to prescribe opioids, often with very short validity periods and pharmacists usually maintain inadequate opioid stocks for the specific needs of the country, because of high storage costs and restrictive legislation (table 1).
It is almost universally accepted that there is a need to find ways to implement safe practices in opioids prescriptions and minimize the risk for abuse and addiction, thereby enhancing patients’ outcomes and reducing costs to patients and to health plan payers [87]. Approaches that will encourage efficiency in the use of opioids may include physician and patient education regarding opioids and their associated abuse risks; the development of prescription monitoring programs to detect inappropriate prescribing and medical errors; the use of physician-patient contracts concerning opioid treatment; the necessity of using photo identification to collect an opioid prescription at the pharmacy; urine drug toxicology screening; provisions for safe disposal of unused opioids; referrals to pain and addiction specialists; and potentially encouraging the use of abuse-deterrent formulations of opioids [88-92].

The availability of opioids in Latin America can be seen in table 2. A more detailed description of all the available formulas of all opioids available in Latin America can be obtained from the manual for Latin America “Use Of opioids in the treatment of pain” published by the Latin American Association of Palliative Care [93]. Table 3 shows the retail sales of some of the opioids on their own or combined with other non-opioid analgesic medications by the local pharmacy stores in Latin American countries (data provided after requesting them by IMS MIDAS MAT in September 2016).

5. Strong opioids for OA pain
The management of OA is a multi-modality process and can be divided in pharmacological and non-pharmacological management where aspects such as education and self-management, exercise and weight loss, assistive devices, some alternative and complimentary approaches (with uncertain appropriateness) (acupuncture, thermal modalities, transcutaneous electrical nerve stimulation and therapeutic ultrasound) and surgical interventions are included [94]. Although this review focuses on a specific pharmacological treatment, it is essential that any treatment for OA should be based on a multimodal approach, where the pharmacological treatments are only a relevant, but not essential, part.

5.1. Guidelines for pharmacological pain management in OA

Most of the current OA management guidelines include recommendations for its pharmacological treatment [94-110]. In all these guidelines, the recommendations are based on the assessment of the benefits of each treatment (not only with respect to pain relief, but also to quality of life and functional improvements) taking into account their side effects as well. The majority of the older guidelines recommended acetaminophen as the first-line treatment of OA pain; but more recent guidelines have slightly changed their attitude towards it: the guidelines of the American Academy of Orthopedic Surgeons (AAOS) no longer recommend it as first line of treatment [99] and the OARSI guidelines recommend it only for patients with low co-morbidities [94]. Also topical NSAIDs followed by oral ones have been recommended as the next most appropriate step. In the same context concomitant gastroprotection is recommended for those patients with a high risk for gastrointestinal complications. Other agents recommended (but not by all the
guidelines) are tramadol [95,99,99] and capsaicin [95,98,102,103,105,110]. For refractory knee OA, duloxetine was recommended in the guidelines of the American College of Rheumatology (ACR) [95] and for the same problem the guidelines of the European League Against Rheumatism (EULAR) recommend antidepressants, sex hormones, herbal remedies and vitamins [105].

For hip and knee OA intra-articular corticosteroids were generally recommended [95,96,98,102,105,110] although the AAOS recommendation is inconclusive [99] and this modality is not recommended by EULAR for hip OA [104]. EULAR guidelines recommend intra-articular corticosteroids for hand OA [103], whereas not by the ones from the ACR [91]. For hip and knee OA the intra-articular hyaluronic acid recommendations by Osteoarthritis Research Society International (OARSI), EULAR and Michigan Quality Improvement Consortium (MQIC) are of low strength, therefore its use remains controversial [98, 104, 105, 110]. The AAOS and the National Collaborating Centre for Chronic Conditions (NCC-CC) do not recommend it [99,102]. Currently there are some promising therapies for very symptomatic knee and hip OA which are still under investigation, such as systemic use of inhibitors of nerve growth factor (tanezumab) [111] or intra-articular treatment with autologous growth factor following injection of platelet rich plasma [112].

5.2 Strong opioids for the pain management in OA

The pertinence of the use of strong opioids for the treatment of chronic OA pain remains unclear and under debate with regards to their efficacy, tolerability and
safety. In 2009 a Cochrane review concluded that non-tramadol opioids should not be used routinely, even in cases with severe OA pain, because their small to moderate beneficial effects were outweighed by the high risk of adverse effects [113]. Despite this, the current guidelines recommend the use of opioids for refractory pain in patients with hip and knee OA [95,98,102,104,105,110], whereas their use is not at all recommended for hand OA [24,95].

The ACR strongly recommends them in patients in whom other medical therapies have failed and have either contraindications or are not willing to undergo total joint arthroplasty [95]. Similarly the MQIC recommends strong opioids as a third line OA treatment in adults [98], when acetaminophen or NSAIDS are ineffective or contraindicated. The National Institute for Health and Clinical Excellence in UK (NICE) concluded that the evidence supporting the use of strong opioid analgesia in OA is poor, there is little evidence to suggest that dose escalation is effective, toxicity and side effects especially in the elderly remain a concern with opioid use and therefore the addition of strong opioid analgesics for pain relief for people with osteoarthritis should be considered only if paracetamol and topical NSAIDs are insufficient [102]. EULAR developed ten key recommendations for the treatment of hip and knee OA based on research evidence and expert consensus: opioid analgesics with or without paracetamol are effective for hip OA, however, the effect may be no better than paracetamol alone and inferior to NSAIDs; therefore, they should only be considered cautiously, when paracetamol or NSAIDs have insufficient efficacy or are contraindicated [104, 105]. OARSI [110] generated twenty-five recommendations regarding hip and knee osteoarthritis based on critical appraisal of existing
guidelines, systematic review of research evidence and the consensus opinions of an international, multidisciplinary group of experts. The recommendations may be adapted for use in different countries or regions according to the availability of treatment modalities. They recommended that strong opioids should only be used for the management of severe pain in exceptional circumstances, whereas weak opioids can be considered for the treatment of refractory pain, where other pharmacological agents have been ineffective or contraindicated.

Schaefert et al [114] in their systematic review of opioids in chronic OA pain concluded that short-term use (4-24 weeks) of opioids may be considered, however they should not be used as a first-line treatment, whereas long-term (>26 months) OA management with opioids should be considered either for patients not suitable for surgical management or to non-responders to other therapeutic modalities. The potential risks of long-term opioid treatment (abuse, increased mortality, fractures) should be carefully balanced against the achieved benefits [115].

5.3. Safe use of opioids in chronic non-cancer pain/OA

In Latin America Burgos-Vargas et al in their study demonstrated that the majority of patients are taking medications throughout the course of the disease; however, only 27% of them take them regularly and on a daily basis; 50% of the OA patients are treated with NSAIDs for their pain and only 10% or less with tramadol/opioids [116], which reflects the current recommendations and the existing fears of opioid misuse/addiction, adverse effects and availability restrictions in Latin America. It
appears that the use of analgesic is dictated by the severity of the symptoms rather than the necessity for consumption on a regular basis. There are important differences in health care utilization and therapeutic features amongst Latin America countries due to the association of OA with ethnicity, living conditions and access/fragmentation of the health care system [117].

In the manual of opioids use for pain treatment in Latin America (referenced by the National Opioid Use Guideline Group of Canada) [93, 118] strong opioids are recommended for the treatment of OA with the aim to alleviate the pain and the return of the patient to a normal activity level [118]. They are indicated for moderate to severe pain >5 in the Visual Analogue Scale (VAS/EVA), which interferes with the functional capacity and QoL of the patient and when the benefits of the treatment exceed the risks [62]. The past medical and family history of the patient should be assessed for drug, alcohol or sexual abuse or dependency and criminal records [89]. When treatment of pain with strong opioids is initiated [62,118,119]: the patient's written consent should be obtained; the dose should be individualized according to the pain intensity of the patient and their age and co-morbidities; the initial dose should be low and should be incremented gradually by 25%-50% every 3-5 days watching for adverse effects, until an optimal effectiveness is reached; fast acting opioids with short half-life are preferable [30]; when the ideal dose is reached then delayed release opioids can be used; breakthrough pain can be managed with rescue doses; assessments of effectiveness and adverse effects should be done regularly and in the cases of high dose requirements, a multidisciplinary evaluation of the patient in the pain clinic should be considered.
The use of opioids is frequently accompanied by adverse effects, even with careful titration of the dose. These side effects often limit the dosing and their effectiveness, leading to under-dosing, inadequate analgesia and even early discontinuation of the treatment [120]. Almost 80% of patients experience one or more adverse effects at the initiation of treatment with opioids, which dictates the necessity for an efficient management of those side effects, thus improving adherence to the treatment [121]. In a systematic review of randomized trials of oral opioids, the commonest adverse effects were dry mouth (affecting 25% of patients), nausea (21%) and constipation (15%), while 22% of the patients on opioids withdrew because of the side effects [122]. Johnson et al in a systematic review of CNCP opioid treatment complications concluded that the most frequently reported adverse effects, such as fatigue, cognitive dysfunction, dry mouth, sweating and weight gain, were 8-fold higher than those reported voluntarily [123].

Opioids, through their actions principally on the gastro-intestinal (GI) opioid receptors in the gut submucosa, reduce gut motility and secretions leading to GI fluid absorption, which causes constipation, for which there is no tolerance on continued use [124] and therefore, it must be anticipated, monitored and addressed throughout the opioid treatment course. It is partially attenuated by using different types of opioid compounds or routes of administration or combining opioids with other medications [120]. Assessment of constipation can be difficult; a questionnaire (Patient Assessment of Constipation) that measures symptom severity (PAC-SYM) and quality of life can be used [120]. There is a need for effective treatment of
opioid-induced constipation. Concomitant administration of laxatives, high fiber content diet, bulk forming agents, adequate hydration, encouraging physical activity, opioid or route administration switch with the initiation or the escalation of the treatment as well as counseling of the patient is strongly recommended to minimize opioid adverse effects [93, 121].

Nausea and vomiting also occur often with initiation or dose escalation; however most patients develop tolerance and persistent effects are infrequent [125]. Antiemetics (e.g. metoclopramide, ondasetron, etc) in the trial phase, slow titration, adequate hydration, opioid or route administration switch with the initiation or the escalation of the treatment as well as patient education are important considerations [125].

Treatment with opioids may cause respiratory depression depending on the dose and the route of administration and therefore, they should be used very carefully in patients with chronic obstructive pulmonary disease (COPD), asthma or emphysema [126]. Careful monitoring of the patient and use of opioid antagonists (naloxone) should be employed to counteract the severe side effect [127]. Central nervous system symptoms like sedation, somnolence, hallucinations, delirium and cognitive and psychomotor changes are not uncommon and they can appear even with low therapeutic doses [128]. Vigilance, dose reduction, naloxone and neurotoxicity family awareness are actions to minimize and combat these complications [93]. Other adverse effects of the opioids include hypogonadism, pruritus, hyperalgesia
and immunosuppression, which might necessitate the discontinuation of the treatment and referral to the specialist [93]. Finally Ray et al showed that opioids, especially the long acting ones, apart from contributing to accidental overdoses, may also contribute to cardiac related deaths and other fatalities and concluded that prescribing long acting opioids was associated with a significantly increased risk of all-cause mortality [129].

Special care should be exercised when using strong opioids for pain relief in elderly patients (the majority of the patients affected by OA). Pain management in the elderly population can be challenging given the concomitant physiological, pharmacological and psychological aspects of their care. Special attention should be paid to the efficacy and side effects of opioids when prescribing to a population with impaired metabolism, excretion, physical reserve and with associated polypharmacy [130]. When treating elderly patients with opioids it is recommended to initiate the treatment with low dose treatment and increase it as tolerated by the patient, use short-acting opioids [30] to start with and switch to maintenance treatment with long-acting ones, include one medication at a time, aim to prevent side effects or treat them rapidly, consider possible interactions with other medications, prescribe simple and easy to follow therapeutic schemes and maintain constantly the patient and their families well informed [93].

Recently there is a lot of interest in opioid medications that may have less side effects (respiratory depression) and lower abuse potential such as buprenorphine, a
partial mu-opioid agonist semi-synthetic strong opioid analgesic [131]. Breivik et al in their 6-months, randomized, controlled trial concluded that a low dose 7-days buprenorphine patch at 5-20 μg/h could be used successfully for pain relief in elderly OA patients, in whom surgery, NSAIDs and COXIBss are not indicated and paracetamol does not provide adequate pain relief [132]. The analgesic effect of transdermal buprenorphine in patients with hip or knee OA, low back pain and other CNCP has been demonstrated in several randomized controlled trials, which compared it with tramadol or codeine plus paracetamol [133]. Buprenorphine has favorable pharmacodynamic and pharmacokinetic properties, is suitable for elderly patients with renal impairment as an once-weekly dose and has good efficacy and tolerability in CNCP [133].

The analgesic effect of opioids is exerted through their binding to the mu-opioid receptor in various areas of the brain, inclusive of the reward regions that underlie the perception of pleasure, which explains the tendency for diversion and abuse of the opioids [134]. In the brain stem the mu-opioid receptors are responsible for the respiratory depression caused by the opioids [126]. A rapid opioid delivery (intravenous) to the brain accentuates their effects, especially the euphoric ones [135]. Their repeated administration leads often to tolerance and physical dependence due to counter-adaptations of the receptors and their intracellular signaling cascades, which resolve rapidly after the cessation of the treatment [136]. On the contrary addiction develops slowly, in a small percentage of patients and its underlying mechanisms evolve much slower, last much longer and disrupt multiple
brain processes, which are associated with structural and functional changes in the reward, inhibitory and emotional circuits of the brain [137].

Currently there is an alarming increase in diversion and improper use of opioids, which has resulted in a worldwide epidemic of opioid overdose deaths and addictions with more than a third of the drug-overdose deaths reported in 2013 attributable to pharmaceutical opioids. [134]. Recently there has been a parallel increase in the rate of opioid addiction, affecting 2.5 million adults in 2014 in the US [138]. The major source of diverted opioids is physician prescriptions [139]. As a consequence physicians are questioning prescribing practices for opioids for chronic pain relief, admit that they are not confident in using opioids, detecting abuse or addiction and discussing these issues with the patients [134]. It has been suggested that by increasing physicians’ and patients’ training on pain and addiction and the use of science-supported prescribing and management practices and pain research, the abuse-related risks can be reduced and the treatment of pain can be improved [134].

The ability of the opioid prescribing physician to detect those patients at risk for developing prescription drug abuse is of fundamental importance [table 4]. Risk factors include sociodemographic factors (young white men and cigarette smoking young women are associated with nonmedical use of prescription opioids), pain and drug-related factors (low pain tolerance, multiple pain complaints, more subjective pain, high daily doses, short-acting opioids appear to increase the risk of abuse),
genetics and environment (variants in the opioid receptors are associated with increased risk of addiction), psychosocial and family history (young age, back pain and substance abuse disorders identify individuals at high risk of misuse), psychopathology (mood disorders, psychological problems and psychosocial stressors), alcohol and substance use disorders (personal history of illicit drug and alcohol abuse and cannabis use are strong predictors of opioid abuse) [140]. Screening for opioid abuse is a good practice and includes assessment of pre-morbid and co-morbid substance abuse, evaluation of aberrant drug-related behaviors, risk factor stratification and utilization of opioid assessment screening tools (urine drug testing, prescription monitoring programs, use of universal precautions) [140].

When treating patients with a history of substance abuse it is very important to adhere to principles which ensure safe and efficient pain management. Only one clinician should be responsible for the patient, a written consent with clear documentation of the treatment plan is vital, the family of the patient and the dispensing pharmacist should be involved, adjuvant non-opioid treatment is recommended, a limited quantity of medication should be dispensed at any one time and spot urine toxicology screening should be included when possible [141].

Before discontinuing an opioid treatment, the length of treatment, the type of the opioid and medical experience should be taken in account [62,118]. It is recommended to reduce the daily dose of the opioid by 25% weekly with close monitoring of the patient. In the case of withdrawal symptoms, 50% of the
previously used daily total dose is reinstituted followed by a smaller percentage of reduction of the daily dose [93].

6. Conclusions

In summary, OA affects a large percentage of the population not only in Latin America but worldwide as well, and its main symptom, chronic pain, is responsible for significant disability amongst OA sufferers, with an important economic burden globally. Although strong opioids are not recommended as a first-line treatment of OA chronic pain by the international and the Latin American guidelines, their use can be valuable in the short-term management of OA cases with moderate to severe pain, where other pharmaceutical modalities have either insufficient effect or are contraindicated and where surgical treatment is also contraindicated. Candidates for treatment with strong opioids should be carefully selected and their personality profile assessed thoroughly before the initiation of treatment. They should be monitored carefully throughout the therapeutic period.

The use of strong opioids is still controversial in Latin America because of restrictions in the availability and prescription of opioids, opiophobia and opio-ignorance amongst physicians and patients. However, it should be kept in mind that strong opioids in Latin America could be a good therapeutic option for OA, counteracting the consequences of limited and delayed access to other therapeutic modalities such as, for example, prosthetic surgery. Educational programs for patients and physicians, further research on treating chronic pain with opioids and
possible use of buprenorphine with its favorable pharmacokinetic and pharmacodynamic profile should be considered and implemented to improve chronic pain management and quality of care.

7. Expert commentary

One of the consequences of increasing life expectancy is an increase in the incidence and prevalence of OA as well. Although significant progress in the understanding of OA pathophysiology has been achieved, the management of OA-mediated pain remains challenging and often insufficient, which affects negatively the quality of life of patients and imposes a significant socioeconomic burden globally. There are many concerns regarding some of the available medications for the treatment of chronic non-cancer pain, such as the cyclooxygenase-2 inhibitors and the anti-inflammatory drugs, due to their significant adverse effects, especially for the elderly population, which is the age cohort to which most of the OA-suffering patients belong. On the other hand, appropriately dosed and monitored use (according to the relevant guidelines) of any opioid, has the potential of being an effective treatment, especially when other therapeutic modalities have failed or are contra-indicated, with fewer life-threatening complications associated, when compared to the more commonly and often less successful employed pharmacotherapeutic approaches.

The problem of the effective management of OA pain is more complex in countries of Latin America, where the availability and use of opioids, especially the strong ones, are governed by strict regulations and the issues of opio-ignorance and opiophobia are equally frequent among pain care professionals and chronic pain suffering
patients. The lack of knowledge among health care professionals on how to use opioids appropriately and adequately (thus controlling and minimizing their adverse effects) and the fear of abuse and dependence among opioid prescribers and opioid users are challenges, which makes the use of opioids for the treatment of chronic non-cancer pain very limited. Similarly stringent laws in Latin American countries regulate the storage and distribution of opioids, which limits their accessibility and delivery, thus affecting negatively the ability of pharmacists to maintain adequate stocks of opioids and at the same time the capability of the health care professionals to prescribe them.

When strong opioids are used within the context of a multimodal and multidisciplinary approach to control pain, they are a safe and effective treatment for joint pain, OA included. Patients may be started on a low dose of opioids and titrated as needed and tolerated. Recently there is a lot of interest in buprenorphine, a partial mu-opioid agonist semi-synthetic opioid with favorable pharmacodynamic and pharmacokinetic properties, which makes it a suitable option for the treatment of OA pain, especially for elderly patients, because of less side effects and lower abuse potential. Educational programs directed not only to health care professionals but to the patients themselves as well, informed consent and the use of an agreement for the use of controlled substance, and at the same time the employment of exercise, weight control and input from complimentary medicine, increase the likelihood of patient compliance with the treatment guidelines, resulting in improved functional capacity and better quality of life.

8. 5 Year View
Osteoarthritis is a degenerative joint disorder, which is encountered very often in the clinical practice, and is the leading cause of disability in elderly people. The lack of specific diagnostic biomarkers and the poor self-healing capacity of articular cartilage, make OA a challenging disease, especially in certain areas of the world such as Latin America, where treatment options are limited. Pharmaceutical therapy is the most commonly used OA treatment option aimed mainly at pain relief and anti-inflammation. However none of the traditional OA drugs can reverse the damage in the OA joint.

Currently there are a number of studies investigating new OA with more effectiveness and fewer side effects, and in addition, regenerative therapy holds the possibility of repairing and regenerating damaged or lost tissue restoring thus the original structure and function. However, still OA in most part of the world is treated with the traditional pharmacological agents: acetaminophen, non-steroidal anti-inflammatory drugs, opioid analgesics, serotonin-norepinephrine reuptake inhibitors and intra-articular injections.

Strong opioids are used to treat moderate-to severe OA pain when other pharmacologic agents are ineffective or contraindicated. Therefore, they are valuable pharmacological agents in the treatment of OA. However, in many areas worldwide, access to strong opioids is limited and/or restricted due to cultural, educational, legislative and availability issues. Programs to educate not only patients and physician regarding the safe use of strong opioids, but all those who are
involved in the use and consumption of opioids should be implemented to optimize their usage for the benefit of the suffering patients. At the same time research should be concentrated in the development of new opioid medication with less side effects for safer and more effective use.

9. Key issues

• Effective treatment of osteoarthritis pain, a disease with high prevalence and affecting mainly elderly patients, remains challenging, controversial and often inadequate.

• Pain due to osteoarthritis is a significant cause of disability with negative effects on quality of life and significant socioeconomic burden, which has a considerable impact on the world’s health care economy.

• Strong opioids might represent an alternative option for the treatment of chronic pain caused by osteoarthritis. The international guidelines recommend their use for the treatment of hip and knee osteoarthritis when other available therapeutic modalities have failed to treat the pain adequately or when they are contraindicated.

• Opioid use can be safe and effective in the treatment of osteoarthritis pain when the guidelines for their use are followed. However their use might be limited in certain areas of the world, and especially in Latin American countries, due to strict laws governing their usage, storage and availability.
• Often both health care professionals and patients are reluctant to use strong opioids to treat osteoarthritis pain due to the lack of knowledge of their therapeutic benefits and how to use them appropriately and safely (opio-ignorance) and because of fear of abuse and dependence (opiophobia).

• Educational programs for health care professionals and patients as well should be employed together with informed consent of the patients to increase awareness of opioid benefits and use to improve pain management, functional status and quality of life.

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conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

**Reference Annotations**


An up-to-date review of the best prescription recommendations available for opioids for chronic non-cancer pain.


A longitudinal multinational study on the prevalence of inadequate pain relief in Europe


An updated review of the risks associated with chronic opioid therapy.


The surgeon’s perspective on the conservative management of knee osteoarthritis.


A group of guidelines for the use of opioids in chronic non-cancer pain, specifically targeting a latinoamerican audience.


A comprehensive review of the available alternatives for the management of osteoarthritis with clear-cut recommendations for each therapeutic option based on the benefits and risks of each alternative.

The “classic” paper on opioid side effects in patients with chronic non-cancer pain.

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<th>Colombia</th>
<th>Costa Rica</th>
<th>Ecuador</th>
<th>Mexico</th>
<th>Peru</th>
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<tr>
<td>Impossible ⁷</td>
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</tbody>
</table>

¹All physicians may prescribe opioids without specific registration.
²Registration is required, but it is not limited to any medical specialty and the administrative process is simple and accessible.
³Prescription is limited to certain medical specialties or the procedure is complex.
⁴Opioids are easily available throughout the national territory and are accessible in all pharmacies.
⁵Opioids are usually available but occasional shortage problems may occur.
⁶The lack of supply is frequent in certain territories. Some pharmacies do not have access to opioids.
⁷In reality there is no access to opioids.

Table 1. Barriers to prescription and dispensing of opioids.
<table>
<thead>
<tr>
<th>Name</th>
<th>Brazil</th>
<th>Chile</th>
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<td>X</td>
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<td>X</td>
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</tr>
<tr>
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<td>X</td>
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<td>X</td>
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<tr>
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<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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</tr>
<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
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Table 2: Opioids availability in Latin America

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>RETAIL SALES Standard units (in thousands)</th>
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</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>135064 (247851)</td>
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<tr>
<td>Morphine</td>
<td>21369 (22347)</td>
</tr>
<tr>
<td>Hydrocodeine</td>
<td>(4414)</td>
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<tr>
<td>Codeine</td>
<td>22344 (231869)</td>
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<tr>
<td>Oxycodone</td>
<td>4703 (4955)</td>
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<tr>
<td>Fentanyl</td>
<td>243</td>
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<tr>
<td>Buprenorphine</td>
<td>3900</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>493</td>
</tr>
</tbody>
</table>

Table 3. Retail sales: standard units (in thousands) of opioid medications in Latin and Central America countries (Brazil, Chile, Colombia Ecuador, Mexico, Peru and Central America). [The IMS standard unit defines a single dose of an opioid medication]. Numbers reflect the total sales of the medications, either on their own or in combination (in parenthesis) with other analgesic medications (paracetamol, NSAIDs, gabapentin, etc.). Source: IMS MIDAS MAT Sept. 2016
<table>
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<tr>
<th>Risk factors</th>
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<td>Sociodemographic</td>
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<tr>
<td></td>
<td>2. Cigarette smoking young women</td>
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<tr>
<td>Pain and drug related</td>
<td>1. Low pain tolerance</td>
</tr>
<tr>
<td></td>
<td>2. Multiple pain complaints</td>
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<tr>
<td></td>
<td>3. More subjective pain</td>
</tr>
<tr>
<td></td>
<td>4. High daily doses of opioids</td>
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<td>5. Short-acting opioids</td>
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<tr>
<td>Genetics and environment</td>
<td>Variants in the opioid receptor</td>
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<td>3. Substance abuse</td>
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<td>1. Illicit drug abuse</td>
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<tr>
<td></td>
<td>2. Alcohol abuse</td>
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<tr>
<td></td>
<td>3. Cannabis use</td>
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Table 4. Risk factors for developing prescription drug abuse.