The Role of Opioids in Chronic Non-Cancer Pain Management

Joseph V. Pergolizzi Jr.¹, Robert B. Raffa², Gianpietro Zampogna³ and Robert Taylor Jr.⁴

¹Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD; Department of Pharmacology, Temple University School of Medicine, Philadelphia, PA; Association of Chronic Pain Patients, Houston, TX, USA
²Department of Pharmaceutical Sciences, Temple University School of Pharmacy, Philadelphia, PA, USA
³NEMA Research, Naples, FL, USA

Abstract: Chronic pain is prevalent in Asia as well as worldwide, and physicians must carefully consider which pharmacologic or non-pharmacologic analgesic strategy is appropriate based on its availability, adverse effects, abuse liability, potential drug-drug interactions, onset of action, tolerability, cost, and—above all—effectiveness. NSAIDs increase the pain threshold by inhibiting cyclooxygenase (COX) and are the first step of the World Health Organization “pain ladder,” but they have been associated with gastrointestinal complications, possible renal failure, and hypertension. Acetaminophen (paracetamol) is an effective pain reliever for mild to moderate pain, but is associated with liver toxicity at high doses. Opioids are effective pharmacologic treatment and standard therapy for moderate to severe cancer pain, but their long-term use for non-cancer pain is controversial. Opioid-associated side effects may be transient, treatable, or treatment limiting. Not all chronic non-cancer pain patients are candidates for opioid therapy, particularly if there are risk factors for misuse or abuse. Combining an opioid and a nonopioid (such as acetaminophen or NSAID) in combination therapy can create synergistic analgesic effect and reduce the patient’s total opioid consumption while still achieving good analgesic results. Adjuvant agents such as anticonvulsants or tricyclic antidepressants can be useful to deal with multimechanistic pain, including pain with a neuropathic component, frequently observed in chronic non-cancer pain patients.

Keywords: Opioid, chronic pain, non-cancer pain, nonsteroidal anti-inflammatory, analgesics.

1. INTRODUCTION

Chronic pain is already a prevalent cause of suffering, and as the populations of Asia and other parts of the world age, it is likely to increase. Unfortunately, chronic non-cancer pain syndromes often go under-treated or even untreated. At no time in history have physicians had more choices in analgesic products, yet they must still carefully consider which pain reliever is most appropriate for an individual non-cancer pain patient. In many cases, there is no perfect pain reliever. Many factors must be considered when prescribing any analgesic agent: its availability, abuse potential drug-drug interactions, onset of action, tolerability (side effects), cost, and effectiveness. While many factors can enter into the prescribing decision, overall effectiveness is paramount. If an analgesic agent cannot effectively relieve the patient’s pain, no other characteristics can make up for this deficit.

Opioids are effective pain relievers, but the role of opioids in the long-term treatment of non-cancer pain syndromes remains controversial [1]. This controversy centers around both a lack of evidence for long-term safety of opioids in this setting [2] and the potential for their inappropriate use [3], which can be an individual problem or a public health concern for communities in which opioids are frequently prescribed. For example, in the United States, where opioid therapy is increasingly accepted for treatment of chronic non-cancer pain syndromes, this shift has resulted in a marked increase in opioid consumption, including inappropriate use [4].

2. PHARMACOTHERAPY

2.1. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

The best way to frame a discussion on the role of opioids in the treatment of moderate to severe chronic non-cancer pain is to understand the role of non-opioid analgesic options. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX), both the constitutive (COX-1) and inducible (COX-2) forms. For example, when a person injures his/her hand, NSAIDs inhibit COX-1 locally and COX-2 induced at both the site of injury (periphery) and the spinal cord (central).[5] They thereby decrease prostaglandin production throughout the body (both peripheral and central sites) and, in so doing, decrease the pain signal. NSAIDs can be roughly categorized as nonselective (those that inhibit both COX-1 and COX-2) and selective (those that inhibit only COX-1 or COX-2); selective COX-2 inhibitors are sometimes called coxibs. NSAIDs can be
particularly effective for relieving prostaglandin-mediated pain states. The World Health Organization (WHO) has recommended the use of NSAIDs for treating cancer pain syndromes on the first step of its well-known “pain ladder” [6]. See Figure 1.

![Figure 1: Representation of the World Health Organization (WHO) pain ladder for the treatment of cancer pain, first introduced in 1988. It progresses from the use of non-opioid analgesics (such as NSAIDs) to opioids as pain intensifies. The WHO pain ladder is often also used as a model for the treatment of non-cancer pain syndromes.](image)

Although NSAIDs can be effective pain relievers for chronic non-cancer pain patients, such as arthritis patients or patients with low back pain, the use of nonselective NSAIDs is limited by gastrointestinal (GI) complications, ranging from mild symptoms (dyspepsia) to symptomatic ulcers, GI bleeding, and even potentially life-threatening perforated ulcers [7]. NSAIDs should not be prescribed to patients at risk for GI complications, although NSAID-associated GI complications may occur in patients with no risk factors.

Nonselective NSAIDs inhibit prostaglandin production in the renal system which can lead to acute renal compromise or failure, fluid and electrolyte imbalances, worsening of pre-existing renal dysfunction, interstitial nephritis and nephrotic syndrome [8]. Although patients with chronic kidney disease should not take NSAIDs, a recent study found that nearly 47% of such patients did take inappropriate drugs, primarily NSAIDs [9]. Selective NSAIDs were once thought to offer a good alternative, but recent findings of cardiovascular risk factors with both nonselective and selective NSAIDs have raised concerns about the wide use of these pain relievers [10]. NSAIDs may raise blood pressure, interfere with antihypertensives (such as beta-blockers and diuretics), and promote fluid retention. NSAIDs have also been linked to excess platelet aggregation, increasing the risk of bruising [11] and interfering with the antiplatelet properties of low-dose aspirin when taken concurrently [12].

While much is known about NSAID toxicity [13]—it has been a leading cause of poisoning in many nations for a decade or longer—silent GI toxicity is a more insidious condition. About 80% of patients with NSAID-associated GI complications have no warning symptoms [14-16]. Therefore, NSAIDs should be used only in selected patients and then at the lowest possible dose for the shortest period of time [17]. NSAIDs should be used under close clinical supervision and with great caution (if at all) in patients with GI risk factors, renal disease, coronary artery disease (CAD), diabetes, liver disease, or those taking anticoagulant therapy. NSAIDs can pose a special risk for the elderly. The American Geriatric Society recommends avoiding or severely limiting the use of NSAIDs in geriatric patients in favor of opioid pain relievers [18], although it appears that cardiovascular risk varies among individual NSAID agents [19]. Certain coxibs (rofecoxib and valdecoxib) have been withdrawn from the U.S. and European markets owing to cardiovascular safety issues.

Nevertheless, for the right patients, NSAIDs offer important advantages; they can be highly effective in the treatment of incidental pain, have a relatively long duration of action, and tend to be effective in controlling pain that is not well controlled by opioid agents. Overall, NSAIDs are reliable and there is little interpatient variability in doses.

### 2.2. Combination Therapy: Non-Opioid Analgesics Plus Opioids

Acetaminophen or NSAIDs can offer synergistic analgesia when combined with opioids and such combinations tend to reduce the patient’s overall opioid consumption by about a third while providing equianalgesia as opioid monotherapy [20, 21]. Many fixed-dose combination products are available on the market and offer a convenient single-tablet dose of both agents. The reduced opioid load may reduce side effects and these combination products are generally well tolerated [21, 22]. While fixed-dose combination analgesic products reduce the pill burden (and in that way may encourage outpatient adherence), only limited product and dose combinations are available. So-called “loose dose” combination therapy can be offered to patients in the form of two or more agents with complementary mechanisms of action. These may be two analgesics (acetaminophen plus an opioid, for example) or an analgesic plus an adjuvant agent such as an anticonvulsant, an antidepressant, or a muscle relaxant.
A notable combination product for management of chronic non-cancer pain is one that combines acetaminophen plus tramadol. Tramadol is a unique opioid agent that has two complementary mechanisms of action: it is a mu-opioid receptor agonist and it also inhibits the neuronal reuptake of noradrenalin (NA) and serotonin (5-HT) [23, 24]. Based on the WHO pain ladder terminology, tramadol would be considered a “weak” opioid and it works synergistically with acetaminophen such that the combined analgesic effect is greater than the sum of its parts.

Tramadol is not associated with prostaglandin-mediated complications, GI toxicity, or nephrotoxicity, nor does it adversely affect platelet aggregation. Tramadol may be safely prescribed to patients on anticoagulation therapy and in sulfa-sensitive patients. In many ways, tramadol can be considered a first-line pain reliever and an alternative to NSAIDs, particularly for patients who are not good candidates for NSAID therapy. Of course, tramadol is associated with some of the same side effects typical of opioid analgesics, but these adverse effects are generally less severe than with “strong” opioids. Tramadol is not a scheduled drug in every country, but it does have a potential for abuse which is higher among those with a history of opioid addiction [25]. Tramadol dependence has been reported in the literature [26].

2.3. Pharmacotherapy for Neuropathic Pain

Chronic pain often involves a neuropathic pain component, associated with aberrant neural activity. Treating chronic non-cancer pain with only non-opioid and/or opioid analgesics may not provide adequate pain relief in that it does not address neuropathic pain mechanisms. Patients typically describe neuropathic pain as shooting, burning, stabbing, or “electrical pain” that can occur, paradoxically, with a concurrent sense of numbness or tingling. Neuropathic pain can be intermittent, may occur paroxysmally, and is sometimes severe. Neuropathic pain can be extremely challenging to treat [27], and, in general, NSAIDs and opioids do not work well for neuropathic pain. Anticonvulsant agents, such as gabapentin, carbamazepine, or phenytoin, may be recommended, but often require prolonged titration periods before their effectiveness can be evaluated. Gabapentin, often considered the first-line neuropathic pain reliever, is an alpha-2-delta subunit calcium-channel blocker that is not metabolized and is excreted by the kidneys unchanged [28]. However, gabapentin-associated side effects may limit treatment in some patients.

Tricyclic antidepressants (TCAs) can also be used to control neuropathic pain, but due to their higher rate of adverse events are typically considered a second-line drug. TCAs achieve their analgesic effect by a combination of NA and 5-HT reuptake blockade [29]. Although low-dose TCAs function mainly as serotonin-reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs) are not as effective in the treatment of neuropathic pain.

2.4. Opioid Agents

Opioid agonists activate 7-transmembrane G protein-coupled receptors (GPCRs) located at central (spinal and supraspinal) and peripheral sites and provide effective analgesia for a range of painful conditions. Numerous opioid agents exist and many of them are available in multiple formulations, ranging from the “gold standard” analgesic of oral morphine to recently developed products such as transdermal buprenorphine, transmucosal fentanyl spray, and buccal fentanyl “lollipops”. Opioid products may be formulated for rapid onset of action or controlled release. WHO’s pain ladder groups opioids roughly into two categories: weak and strong. This terminology is not used much today; it is now more common to categorize by the dose and formulation of the opioid agent.

Overall, it can be said that opioids are associated with a range of side effects that include, but are not limited to, nausea and vomiting, dizziness, constipation, dry mouth, somnolence, and depressed libido. Many of these adverse events can be managed; some diminish with time. Patients who do not tolerate one opioid may tolerate another opioid at an equivalent dose; therefore, it may be useful to “rotate” opioids for patients experiencing side effects before discontinuing opioid therapy. However, some opioid-associated side effects can be treatment limiting.

Opioids should only be administered when the patient is aware of both the risks and potential benefits of opioid therapy. In some cases, clinicians may want to write out the risks and specify the responsibilities of both patient and physician in the form of an agreement prior to starting therapy [30]. The purpose of such a document is to be clear and straightforward about what is expected (for example, that patients will take the
In selecting patients for opioid therapy, clinicians must consider risk factors for opioid misuse or abuse [31-33]. These risk factors can change with time, so they should be periodically re-assessed [34]. In general, patients who have a history of substance abuse or those with mental health disorders are at elevated risk for future opioid misuse. This does not mean that such individuals do not have legitimate pain syndromes or that they must be denied adequate analgesia. Pain relief should be considered a human right [35]. But these patients may require close clinical supervision, consistent education, or alternative analgesic therapies (which go beyond the scope of this article).

2.4.1. Commencing Opioid Therapy

If opioid analgesia is appropriate for a particular patient suffering from moderate to severe chronic non-cancer pain, the clinician must first determine if the patient is opioid experienced or opioid naïve. For the opioid naïve patient, the clinician should begin therapy with the lowest dose (offering supplemental non-opioid pain relievers if needed) and titrate every three to seven days. During the titration phase, the clinician should be watchful for potential opioid-associated side effects or misuse [36]. Patients should be educated to side effects and encouraged to report them, so that they can be managed as effectively as possible.

Opioid-experienced patients are those who are currently taking opioid analgesics. Using a conversion tool, the clinician should determine the patient’s current daily dose of opioid and calculate the appropriate dose of the alternate opioid. The new opioid should be started at a percentage of that total dose (because of incomplete cross-tolerance) and titrated every three to seven days until optimal analgesia is achieved. It is important to note that equianalgesic tables are not precise tools, they offer broad guidance only [37].

When titrating opioid doses for chronic pain patients, clinicians should be mindful that the dose for optimal analgesic efficacy can vary widely even among seemingly similar pain conditions or patients.

2.4.2. The Role of Long-Acting Opioids

Long-acting or extended-release opioid formulations offer some important features that may potentially benefit chronic pain patients. Long-acting agents reduce the pill burden, which may improve patient adherence [38]. Long-acting formulations administered by a fixed-clock schedule can close so-called “analgesic gaps” or the period where the drug’s serum concentration falls very low prior to the next dose. In the case of opioids, long-acting formulations may also prevent “mini-withdrawals” during this period.

Immediate-release opioid formulations are often used to initiate therapy or for acute pain syndromes. For chronic pain conditions, extended-release formulations are usually more convenient.

2.5. Rescue Medication

Although the term “breakthrough pain” is more commonly used with reference to cancer patients, non-cancer pain patients may also experience sudden excursions of severe to very severe pain against an ambient background of controlled pain [39]. In a study of 228 non-cancer chronic pain patients, 189 different types of breakthrough pain were identified [39]. The ideal rescue medication would have an extremely rapid onset of action and be strong enough to control severe or very severe pain. Oral opioids are often used for rescue medication, but they might have a delayed onset of action or the oral bioavailability of an agent might be less than the parenteral version. New rapid-acting formulations, such as transmucosal fentanyl, are being introduced and may come to play an important role for management of severe breakthrough pain episodes.

As a rule of thumb, rescue medication should be a fraction of the daily dose of opioids, for example, one-sixth to one-third of the 24-hour dose. Clinicians should discuss rescue medication with their patients to determine if rescue doses should be increased or decreased. Patients who need frequent rescue medication without obvious reason such as disease progression or tolerance should be considered for a dose adjustment.

2.6. Opioid-Associated Side Effects

Appropriate management of opioid-associated side effects may be a crucial component in successful long-term opioid therapy [40]. Therefore, clinicians should anticipate opioid-related adverse effects and educate patients about them. Certain opioid-associated side effects may be transient (e.g., nausea, vomiting, pruritus, sedation, respiratory depression, or urinary retention) but others tend to persist (e.g., constipation, diaphoresis, dependence, or impotence/decreased
Specific effects, such as cognitive or psychomotor impairment (“foggy thinking”) may be transient in some patients, but persistent in others [41]. Persistent cognitive dysfunction and other distressing side effects may limit treatment [42].

Many opioid-related side effects can be managed. For example, antiemetics can treat nausea and vomiting. A bowel regimen can be commenced with the start of opioid therapy to manage constipation and ileus. The incidence of constipation may vary by type of opioid used, for example, tapentadol has a lower incidence of GI adverse effects than other opioids, such as morphine [43].

When assessing apparent adverse effects, it is important to consider that not every reported side effect is associated with the opioid. The patient’s underlying disease, comorbid conditions, or treatments (including other drugs) may provoke symptoms. For example, chronic pain may, in and of itself, cause fatigue, somnolence, and cognitive dysfunction apart from opioid therapy. Many drugs, not just opioids, are associated with side effects such as dizziness or nausea.

It should also be noted that reducing pain intensity improves behavioral and cognitive dimensions [44]. Adequate pain control might improve mood and the patient’s sense of well-being as well. Thus, opioids may be associated with positive effects in terms of the patient’s holistic well-being, mood, or functional status.

2.7. Transdermal Opioids

Buprenorphine and fentanyl are available in transdermal delivery systems. Transdermal opioids offer certain important advantages: they are convenient, reduce adherence issues, can be used in patients with dysphagia [45] or who dislike other routes of administration, and offer a long-acting effect. Transdermal opioids are currently indicated only for opioid-experienced patients who need continuous, round-the-clock opioid analgesia for a prolonged period of time.

Transdermal fentanyl is a potent opioid agonist with a gradual onset of action (about 12 hours), achieving steady-state at around 16 hours, and duration of action ranging from 48 to 72 hours [46]. Fentanyl is 75- to 100-times more potent than morphine, might produce less constipation than other opioids, but may increase sedation [47]. Even when the goal is to use transdermal fentanyl, patients should commence opioid therapy with oral morphine or another opioid agent before being rotated to transdermal fentanyl.

3. LIMITATIONS OF OPIOID THERAPY FOR CHRONIC NON-CANCER PAIN

The perfect pain reliever has not been invented. Opioid therapy can be appropriate and provide meaningful pain relief to certain chronic non-cancer patients, but opioids are certainly not appropriate for all non-cancer pain patients. Opioid-associated side effects remain one of the most frequent reasons for limiting opioid therapy. Unfortunately for clinicians, the nature, severity, and likelihood of adverse events is difficult to predict. Opioid rotation should be considered before discontinuing therapy, because a patient experiencing distressing side effects with one opioid may tolerate another opioid very well [48].

The unpredictability of opioid effectiveness can be another limitation to opioid therapy, in that there is considerable variation in treatment response among patients. In a study of patient-controlled morphine for postsurgical pain, 40.4% of patients were classified as “non-responders” to morphine [49]. Thus, clinicians prescribing morphine to chronic pain patients for long-term use must be prepared to work closely with the patient to find the correct opioid and titrate the optimal dose. There is no easy formula to identify the appropriate dose for a given patient; even seemingly very similar pains or patients may require markedly different doses for adequate control.

Opioids are highly effective analgesics for many types of pain, but they have limitations. For instance, they do not work well on incident pain (such as pain with movement) or neuropathic pain.

Finally, a major consideration for many clinicians and communities is the potential for misuse of opioid pain relievers. While risk factors for opioid misuse can be reduced, they can never be completely eliminated. [50] Proper patient selection, initial and ongoing patient education, close clinical supervision, treatment agreements [51], urine drug testing, [52] and abuse-deterrent formulations [53] are all important tools that can reduce the inappropriate use of opioids. The Singapore Task Force on the Use of Opioids in Chronic Non-Cancer Pain do not advocate opioids as a first-line treatment for musculoskeletal chronic pain syndromes but allows that they may be considered if other analgesic agents are ineffective [54].
Table 1: Summary of Guidelines for the Treatment of Chronic Pain Syndromes Associated with Hip or Knee Osteoarthritis [56]

<table>
<thead>
<tr>
<th>Guideline</th>
<th>APAP</th>
<th>Nonselective NSAIDS</th>
<th>Coxibs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>EULAR 2005</td>
<td>1st</td>
<td>2nd with PPI for those at elevated GI risk</td>
<td>2nd for patients with elevated GI risk</td>
<td>For disease refractory to or inappropriate for other agents</td>
</tr>
<tr>
<td>NICE 2008</td>
<td>1st</td>
<td>2nd with PPI</td>
<td>2nd with PPI</td>
<td>2nd</td>
</tr>
<tr>
<td>AAOS 2008</td>
<td>1st</td>
<td>1st with PPI for those at elevated GI risk</td>
<td>1st for patients with a history of GI bleeding or current steroid or anticoagulation therapy</td>
<td>No recommendation</td>
</tr>
<tr>
<td>OARSI 2010</td>
<td>1st</td>
<td>1st for moderate to severe pain; 2nd for mild to moderate pain</td>
<td>2nd for patients with elevated GI risk</td>
<td>2nd</td>
</tr>
<tr>
<td>ACR 2012</td>
<td>1st</td>
<td>2nd in patients under 75 years with no GI bleeding in past year</td>
<td>2nd for patients with &gt; 1 year history of GI bleed or ulcer; 3rd for patients &gt; 75 yr</td>
<td>2nd with tramadol specifically recommended for patients 75 yr with disease refractory to or inappropriate for other agents</td>
</tr>
</tbody>
</table>

Abbreviations: AAOS = American Academy of Orthopedic Surgeons; ACR = American College of Rheumatology; APAP = acetaminophen; EULAR = European League against Rheumatism; GI = gastrointestinal; NICE = National Institute for Health and Care Excellence; OARSI = Osteoarthritis Research Society International; PPI = proton pump inhibitor; yr = years

4. PRACTICAL MANAGEMENT OF CHRONIC NON-CANCER PAIN SYNDROMES

For patients with mild to moderate musculoskeletal pain, acetaminophen (maximum 4 grams/day total from all sources) should be considered the front-line approach. NSAIDs, even coxibs, should be avoided owing to cardiovascular, GI, and renal risks. If acetaminophen is not effective within the therapeutic dose range, the second-line drug of choice can be a fixed-dose combination product of acetaminophen plus tramadol, then tramadol monotherapy, and possibly other opioid agents [55].

For patients with persistent moderate to severe musculoskeletal pain syndromes, the baseline analgesic regimen for constant pain depends on whether the patient is young and healthy or frail and elderly. For young and healthy patients, the baseline regimen should start with acetaminophen/tramadol combination or coxibs/NSAIDs (at the lowest effective dose); as pain intensifies, tramadol monotherapy or even strong opioids can be used. For the frail elderly, the baseline regimen should start acetaminophen/tramadol combinations, and then progress to tramadol monotherapy or other opioids as pain worsens, circumventing the use of NSAIDs [55]. A summary of guidelines for the management of chronic pain associated with hip or knee osteoarthritis is shown in Table 1.

CONCLUSION

Opioids can play an important role in the management of moderate to severe chronic non-cancer pain syndromes in selected patients, but not all patients are appropriate candidates for opioids, so clinical caution is advised. If appropriate, opioids should be introduced slowly and under close supervision to titrate the optimal effective dose. In many cases, opioid rotation may be recommended to improve tolerability and maintain effectiveness. As practical advice, clinicians should first consider nonopioid therapy (being mindful of the important risks associated with them), consider multimodal therapy and the use of adjuvant agents, and educate the patient to set realistic goals in terms of pain management.

REFERENCES


palliative/painladder/en'.


