Review
Complexities in the pharmacologic management of osteoarthritis pain

Bill McCarberg
University of California San Diego, San Diego, CA, USA

Penny Tenzer
University of Miami, Miller School of Medicine, Department of Family Medicine, Miami, FL, USA

Address for correspondence:
Bill McCarberg MD FABPM, Assistant Clinical Professor, Adjunct, University of California San Diego, Suite 380, 16855 W. Bernardo Drive, San Diego, CA 92127, USA.
Tel.: +1 858-312-5234; Fax: +1 858-312-5234; rundbillrun@cox.net

Keywords:
Acetaminophen – Musculoskeletal – NSAIDs – Opioids – Osteoarthritis – Practice guidelines

Abstract
Objective:
To discuss challenges in the pharmacologic management of osteoarthritis (OA) pain.

Scope:
Literature searches through MEDLINE and Cochrane databases were used to identify relevant journal articles. The search was limited to articles published from January 1982 to January 2013. Additional references were obtained from articles extracted during the database search.

Findings:
Pharmacologic management of OA is aimed at alleviating pain and reducing functional impairment. Limitations of the most commonly prescribed agents (non-steroidal anti-inflammatory drugs [NSAIDs], acetaminophen, and opioids) and conflicting practice guidelines have led to physician and patient dissatisfaction. OA management guidelines advocate the use of acetaminophen, NSAIDs, serotonin-norepinephrine reuptake inhibitors (SNRIs) and opioids; however, these agents are associated with serious adverse events (AEs) and, in some cases, efficacy concerns. Acetaminophen, particularly at higher dosages, may lead to acute liver failure and gastrointestinal (GI) bleeding. NSAIDs present a significant GI bleeding risk and are also associated with a variety of renal complications, myocardial infarction and other serious cardiovascular complications. SNRIs can cause AEs such as hepatotoxicity and drug-drug interactions that can lead to serotonin syndrome. Opioids exhibit abuse potential and tramadol may demonstrate limited efficacy.

Conclusions:
The safety and efficacy concerns associated with currently available OA treatment options establish a need to develop new treatment strategies. Disease-modifying agents and novel drug formulations are currently under investigation. As these new pharmacologic options evolve, their adoption may lower risk and improve clinical outcomes.

Introduction
Osteoarthritis (OA) is the greatest cause of disability and chronic pain in adults. In the United States alone, an estimated 27 million adults over the age of 25 years suffer from the potentially debilitating symptoms of OA. The disease prevalence is escalating in the United States, with the number of patients with OA increasing by 6 million from 1995 to 2006. Incidence increases with age, but OA is not solely a disease of the elderly – genetics and joint injury can prompt early disease development and progression in young patients. With approximately $89 billion spent annually, OA management is costly to the health care system.

OA is characterized by articular symptoms secondary to cartilage destruction and a subsequent tissue response. Clinical manifestations of OA include,
but are not limited to, joint pain and stiffness resulting in functional impairment. OA follows an intermittently progressive course with therapeutic strategies aimed at improving quality of life by actively addressing functional impairment and pain. Disease-modifying agents are not currently available, limiting therapy to symptomatic treatment. For decades, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids have been the most widely prescribed agents in OA management. Studies have shown that tricyclic antidepressants effectively manage OA symptoms, and a serotonin/norepinephrine reuptake inhibitor, duloxetine, was approved recently for the management of chronic musculoskeletal pain. However, OA management is complicated by the limitations of the most commonly prescribed treatment options. Uncertainty surrounding the safest and most effective pharmacologic OA management options has led to physician and patient dissatisfaction, unmet clinical needs, and escalating health care costs.

OA management is largely site specific. Destruction of the weight-bearing hip and knee joints can drastically reduce functional capacity and has the most significant clinical impact. This review will focus on the clinical challenges of managing OA pain of the knee and hip with acetaminophen, NSAIDs, opioid analgesics, and other approved pain medications, including tramadol and duloxetine.

**Methods**

We used automated literature searches through MEDLINE and Cochrane databases to identify relevant journal articles published from January 1982 to January 2013. We used search terms with high sensitivity and low specificity to reduce the possibility of oversight. Key search terms included: osteoarthritis, osteoarthritis guidelines, opioid osteoarthritis, NSAID osteoarthritis, acetaminophen osteoarthritis, osteoarthritis management, osteoarthritis prevalence, opioid abuse, acetaminophen hepatotoxicity, and NSAID adverse events. We obtained additional references from articles extracted during the database search.

**Principles of osteoarthritis management**

Population studies have estimated that 6.7% to 16.7% of adults ≥ 45 years of age have symptomatic knee OA and 9.2% of adults ≥ 55 years of age have symptomatic hip OA. From 2002 to 2005, an estimated 22.5 million patients sought treatment for OA. An estimated 80% of patients diagnosed with OA are managed by primary care providers (PCPs), who constitute the largest proportion of physicians caring for this population. However, ongoing management can be complex. Cartilage is weakly innervated, so radiographic findings consistent with OA may not present as clinically relevant symptoms. As such, there is often discordance between the severity of radiographic findings and the severity of symptoms, linking management strategies to reduction in pain intensity. Functional capacity assessments, which also guide treatment, are inexorably coupled to pain intensity. Prospective and retrospective studies have established a clear association between OA pain and functional capacity. In a study performed by Jordan et al., moderate or severe OA knee pain was associated with difficulty in the completion of all categories of the Health Assessment Questionnaire.
(NHANES) demonstrated that baseline OA knee pain was associated with increased risk of developing functional impairment up to 13 years later\textsuperscript{17,18}.

It is apparent that OA management strategies are focused largely on clinical presentation. Symptom-based approaches prevent unnecessarily aggressive therapeutic regimens\textsuperscript{18} and effective pain relief can have a direct and substantial impact on clinical outcomes\textsuperscript{19}. Unaddressed inflammation, through the release of inflammatory mediators, directly impacts disease progression and persistence. The mechanical dysfunction and tissue damage resulting from OA can trigger neuronal hyperexcitability at sites of inflammation, prompting increased central and peripheral sensitivity. Activation of these neural pathways may play a role in the development, degree, and types of chronic pain. Persistent activation of adaptive and innate immune responses can also play a role in disease progression\textsuperscript{20–22}.

The presence of acute or chronic pain in OA may have direct psychological effects—inducing anxiety, depression, somnolence, or difficulty sleeping. This emotional lability can negatively affect interpersonal relationships, further reducing quality of life\textsuperscript{23}. Patients with arthritis who participated in the NHANES III survey (2001–2002) reported greater impairments in quality of life than patients with cancer\textsuperscript{24}. In the elderly, a population with the most substantial OA disease burden, inadequate pain management is associated with reductions in quality of life and functional level, as well as increased financial burden\textsuperscript{25}.

The socioeconomic, psychological, and pathophysiological impact of OA pain is of considerable clinical concern\textsuperscript{26}. Shifting prescription practices highlight widespread uncertainty, as well as dissatisfied clinicians and patients. A 2003 retrospective study by Gore \textit{et al.}\textsuperscript{27} analyzed data from 18,184 patients with OA and found that an estimated 84% to 93% discontinued their first medication within 1 year following administration, and approximately 30% to 60% of patients switched agents within a year. The pattern of ongoing switching among NSAIDs has also been examined. Walker \textit{et al.}\textsuperscript{28} assessed data from 13,965 OA patients and determined that 33% of NSAIDs were exchanged for other members of the class within 60 days due to lack of efficacy, and 13% were exchanged secondary to toxicity. Reflecting the lack of sufficient therapeutic options, polypharmacy is a familiar presence in OA, with patients commonly prescribed multiple agents concomitantly\textsuperscript{29}. These studies emphasize the dissatisfaction with long-term use of OA prescriptions and treatment outcomes.

Additional concern regarding OA management is, in part, a response to the withdrawal of the COX-2 inhibitors rofecoxib and valdecoxib from the market\textsuperscript{12}. Selective COX-2 inhibitors were designed to reduce the risk of NSAID-related gastrointestinal (GI) adverse events (AEs) through decreased activity of COX-2, an isoenzyme with strong GI AE associations\textsuperscript{30}. Following their approval in the United States, COX-2 inhibitor use rose dramatically, from 35% of patients taking any NSAID in 1999 to 61% in 2001\textsuperscript{31}. However, COX-2 inhibitors are linked to myocardial infarction (MI) and other serious cardiovascular (CV) events\textsuperscript{30}. With the exception of celecoxib, all selective COX-2 inhibitors were ultimately withdrawn from the US market, impacting prescription practices and highlighting the need for pharmacologic alternatives in OA pain management\textsuperscript{31–33}.

Fundamentally, the OA treatment paradigm stems from an emphasis on drug-related complications, exemplified by the controversy surrounding COX-2 inhibitors\textsuperscript{12}. The elderly are especially susceptible to AEs associated with acetaminophen, NSAIDs, and opioids\textsuperscript{23}. Physician concern regarding drug-related complications and the apparent inadequacy of disease management has incited growing reliance on consensus practice guidelines. Widespread adoption of clinical guidelines may reduce health care costs and improve care by streamlining drug utilization and limiting the persistence of ineffective treatment strategies\textsuperscript{34}. However, it is critical to distill guidelines through a filter of novel health care claims to provide clinicians with current and effective management strategies\textsuperscript{35}.

**Current guidelines in the management of osteoarthritis**

The CDC’s current OA Public Health Agenda emphasizes the access to and adoption of evidence-based interventions\textsuperscript{5}, OA treatment guidelines have been independently developed by the American Academy of Orthopedic Surgeons (AAOS), the American College of Rheumatology (ACR), the National Institute for Health and Clinical Excellence (NICE), the European League Against Rheumatism (EULAR), and the Osteoarthritis Research Society International (OARSI) (Table 1). These recommendations present a heterogeneous series of therapeutic strategies for the management of OA. The existence of multiple guidelines with contrasting recommendations makes evidence-centered, guideline-based patient management challenging. All of the guidelines advocate early use of acetaminophen, citing its clinical efficacy and relatively benign side-effect profile. AAOS and OARSI both recommend the first-line use of oral NSAIDs, but the AAOS guidelines stipulate the use of adjunctive gastroprotective agents, and OARSI limits NSAID use to patients with moderate-to-severe pain presentations. Guidelines from the other groups recommend oral NSAIDs for patients unresponsive to acetaminophen therapy. NICE guidelines advocate co-administration of
proton pump inhibitors (PPIs) in all patients receiving NSAIDs. OARSI and ACR limit adjunctive PPI use to patients at increased risk for development of GI AEs. All groups limit the use of selective COX-2 inhibitors and topical NSAIDs as second-line agents, except AAOS, which advocates first-line use.

Opioid use is largely restricted to managing pain that is refractory to alternative pharmacologic options. The NICE guidelines support opioid administration for patients unresponsive to acetaminophen alone, while the ACR guidelines conditionally recommend tramadol use in patients ≥75 years of age who have failed acetaminophen therapy. Additionally, the ACR suggests duloxetine administration in patients ≥75 years of age who have failed acetaminophen therapy.

### Table 1. Evidence-based guidelines in the pharmacologic management of OA of the knee and hip.

<table>
<thead>
<tr>
<th>Society (Year)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acetaminophen</strong></td>
<td></td>
</tr>
<tr>
<td>EULAR (2005)</td>
<td>First-line agent</td>
</tr>
<tr>
<td>NICE (2008)</td>
<td>First-line agent</td>
</tr>
<tr>
<td>AAOS (2008)</td>
<td>First-line agent</td>
</tr>
<tr>
<td>ACR (2012)</td>
<td>First-line agent</td>
</tr>
<tr>
<td><strong>Non-selective Oral NSAIDs</strong></td>
<td></td>
</tr>
<tr>
<td>AAOS (2008)</td>
<td>First-line agent in patients &lt;75 years of age without a history of GI bleeding within the last year</td>
</tr>
<tr>
<td>ACR (2012)</td>
<td>Second-line agent in patients ≥75 years of age without a history of GI bleeding within the last year</td>
</tr>
<tr>
<td>NICE (2008)</td>
<td>Second-line agent that should be co-prescribed with a PPI</td>
</tr>
<tr>
<td>EULAR (2005)</td>
<td>Second-line agent that should be co-prescribed with a PPI</td>
</tr>
<tr>
<td>OARSI (2010)</td>
<td>First-line agent in moderate-to-severe OA pain; second-line agent in mild-to-moderate OA pain</td>
</tr>
<tr>
<td><strong>Selective COX-2 Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>AAOS (2008)</td>
<td>First-line agent in patients with a history of PUD and GI bleeding or concurrent corticosteroid or anticoagulant use</td>
</tr>
<tr>
<td>ACR (2012)</td>
<td>Second-line agent in patients with more than a 1-year history of symptomatic or complicated GI bleed or ulcer and third-line agents in patients ≥75</td>
</tr>
<tr>
<td>NICE (2008)</td>
<td>Second-line agent that should be co-prescribed with a PPI</td>
</tr>
<tr>
<td>EULAR (2005)</td>
<td>Second-line agent in patients with increased risk for GI AEs</td>
</tr>
<tr>
<td>OARSI (2010)</td>
<td>Second-line agent in patients with increased risk for GI AEs</td>
</tr>
<tr>
<td><strong>Topical NSAIDs</strong></td>
<td></td>
</tr>
<tr>
<td>AAOS (2008)</td>
<td>First-line agent in patients with a history of PUD and GI bleeding or concurrent corticosteroid or anticoagulant use</td>
</tr>
<tr>
<td>ACR (2012)</td>
<td>Second-line agent in OA of the knee</td>
</tr>
<tr>
<td>NICE (2008)</td>
<td>First-line agent</td>
</tr>
<tr>
<td>EULAR (2005)</td>
<td>Demonstrate safety and clinical efficacy</td>
</tr>
<tr>
<td>OARSI (2010)</td>
<td>Adjunctive or alternative treatment to oral NSAIDs</td>
</tr>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
</tr>
<tr>
<td>AAOS (2008)</td>
<td>No recommendation</td>
</tr>
<tr>
<td>ACR (2012)</td>
<td>Tramadol is a second-line agent in patients ≥75. All other opioids are limited to management of disease refractory to management with other agents in patients who are not candidates for joint arthroplasty</td>
</tr>
<tr>
<td>NICE (2008)</td>
<td>Second-line agent</td>
</tr>
<tr>
<td>EULAR (2005)</td>
<td>Management of disease refractory to, or inappropriate for, management with other agents</td>
</tr>
<tr>
<td>OARSI (2010)</td>
<td>Management of disease refractory to, or inappropriate for, management with other agents</td>
</tr>
<tr>
<td><strong>Duloxetine</strong></td>
<td></td>
</tr>
<tr>
<td>ACR (2012)</td>
<td>Second-line agent in patients ≥75</td>
</tr>
</tbody>
</table>

1AAOS does not provide guidelines for managing OA of the hip.

2Use with gastroprotective agent in patients at increased risk for GI events.

3Use with proton pump inhibitor in patients with a history of GI bleed within the past year.

4No specific recommendations.

OA = osteoarthritis; GI = gastrointestinal; PPI = proton pump inhibitor; PUD = peptic ulcer disease; AE = adverse event; AAOS = American Academy of Orthopedic Surgeons; ACR = American College of Rheumatology; NICE = National Institute for Health and Clinical Excellence; EULAR = European League Against Rheumatism; OARSI = Osteoarthritis Research Society International.

### Barriers to adequate osteoarthritis management

Medical societies espouse the value of patient-centered treatment strategies in disease management. Clinical success is contingent on individually tailored treatment plans, driven by relevant medical history. Pain relief and the subsequent impact on quality of life is the cardinal construct of OA management. Failure to provide adequate analgesia can negatively impact patient outcomes and increase hospitalization rates.

Current OARSI, AAOS, NICE, EULAR, and ACR guidelines recommend analgesia-based dose titrations of acetaminophen up to a maximum dose of 4 g/day. This upper-limit value is largely derived from historical data.
demonstrating hepatotoxicity at acetaminophen doses of >4 g/day. However, the safety of acetaminophen, when dosed at its recommended upper limit, is not straightforward. Acetaminophen is the most common cause of acute liver failure in the United States, and is associated with an estimated 26,000 hospitalizations and 458 deaths per year. However, 14% to 30% of acetaminophen-induced hepatotoxicity cases have been linked to unintentional therapeutic misuse. These cases are often attributable to concomitant alcohol abuse or liver disease, and over-the-counter drug polypharmacy.

In January 2011, highlighting the significant morbidity associated with improper and unsupervised acetaminophen use, the Food and Drug Administration (FDA) limited the permissible concentration of acetaminophen in prescription drug products, including combination pain medications that contain hydrocodone and oxycodone, from 650 mg to 325 mg per dose unit, and instituted a boxed warning emphasizing the risk of liver failure.

Various medical organizations and the FDA have suggested limiting the maximum daily dose to 3 g/day. In 2011, Johnson & Johnson’s McNeil Consumer Healthcare voluntarily reduced the maximum daily dosage of its acetaminophen 500 mg products to 3 g/day and acetaminophen 325 mg products to 3.25 g/day. However, most generic acetaminophen products have not reduced the maximum daily dosage from 4 g/day.

Investigations also suggest that acetaminophen, at elevated doses, may place patients at risk for upper GI complications. In a case–control study of 958,397 subjects receiving acetaminophen at ≥2 g/day, Garcia Rodriguez and Hernandez-Diaz identified a relative risk (RR) of 3.6 for upper GI complications. Furthermore, Rahme et al. observed elevated hospitalization rates for GI complications in patients receiving acetaminophen at >3 g/day.

Acetaminophen may also be associated with an increased risk of CV complications. In a large prospective study, Chan and colleagues demonstrated a dose-dependent relationship between acetaminophen and CV AEs (MI, stroke, congestive heart failure exacerbation, and CV-related deaths). Furthermore, researchers have documented a detrimental influence of ongoing use of acetaminophen on blood pressure. A prospective cohort study in 16,031 patients identified a 1.34 RR for the development of hypertension in patients using acetaminophen ≥6 days per week. It has also been demonstrated that acetaminophen use 22 days per month is associated with a 2.00 RR for the development of hypertension in one study and a 1.20 RR in another.

Additional studies are needed to further understand which patient populations would be at greatest risk for developing such treatment-related complications. The current designation of acetaminophen as a first-line agent is not solely based on safety, but also its efficacy in managing OA. Several studies indicate that acetaminophen provides effective pain relief that is comparable to NSAIDs. Despite safety concerns, lower doses of acetaminophen represent an analgesic option for many patients, especially the elderly.

**NSAIDs**

Reconciling the safety and efficacy concerns regarding oral NSAIDs with current OA treatment guidelines is equally challenging. Oral NSAIDs are associated with significant GI, CV, and renal AEs. Across the class, there is a proportional increase in the development of AEs associated with increased NSAID dose. Mounting concern regarding the safety and tolerability of oral NSAIDs prompted the FDA to release a Public Health Advisory, class labeling template, and physician-education initiative in 2005. Oral NSAID-related GI complications alone comprise a significant percentage of all medication-related AEs. NSAIDs are associated with a five-fold increased risk for the development of peptic ulcer disease and peptic-ulcer-related complications, including perforation and hemorrhage. These serious upper GI injuries account for 34% of all medication-related AEs and are responsible for 3200 deaths annually in the United States. Co-administration of gastroprotective agents can reduce GI AE risk, a costly alternative that is not without persistent risk. Oral NSAIDs are also associated with the development of serious disease of the small and large intestine, such as stricture, bleeding, and perforation.

As previously noted, selective COX-2 inhibitors developed to reduce GI AE risk were associated with serious CV events, prompting the withdrawal of all but one from the market. Non-selective NSAIDs are also associated with serious CV AEs, though to a lesser extent. NSAIDs have been associated with MI, stroke, hypertension, exacerbation of chronic heart failure, and CV death. In a nested case–control study performed by Kaiser Permanente covering 2,302,029 person-years, ibuprofen and naproxen were associated with an odds ratio of 1.26 and 1.36, respectively, for the development of MI. In a retrospective analysis of 4765 patients with stroke, the RR for the development of first stroke in patients receiving NSAIDs was 1.2 compared with NSAID-naïve patients. A meta-analysis by Trelle et al. identified CV mortality rate ratios of 2.39 and 2.07 for ibuprofen and celecoxib, respectively, compared with placebo. NSAID-related nephrotoxicity is at least partially responsible for these CV manifestations. In a study performed by Schneider and colleagues, 4228 new NSAID users over the age of 65 years were matched with 84,540 controls and adjusted for age. Naproxen >750 mg was associated with a 3.62 RR for acute renal failure hospitalization. A prospective trial conducted by the University of Calgary demonstrated a 26% increased risk for the development of chronic
kidney failure in patients receiving high-dose (cumulative dose ≥90th percentile) NSAIDs. NSAIDs are also associated with a diverse array of renal complications, including electrolyte abnormalities, fluid retention, nephrotic syndrome, interstitial nephritis, and renal papillary necrosis.

The FDA recommends the use of NSAIDs for the shortest duration consistent with patient treatment goals; however, NSAID-related GI and CV AEs (and some renal AEs) can occur at any time following administration of NSAIDs. A pivotal retrospective analysis by Schjerning et al. established that duration of NSAID exposure is not an accurate predictor of CV risk and there is no safe therapeutic period following NSAID administration in patients at risk for CV events. A case-control study of 138,949 subjects supports these findings, indicating that both short- and long-term NSAID exposure is associated with MI. Similarily, GI complications can develop within days following NSAID use and renal complications can occur within hours. Of additional clinical concern, greater than 60% of men and 70% of women ≥65 years of age suffer from OA, a population at increased risk for the development of NSAID-related complications. However, the efficacy of NSAIDs for potent pain relief in OA is well established. Although NSAIDs are rife with safety concerns, intermittent dosing for the patient in pain is one of many alternatives available.

Some commercially available agents have been developed to improve the safety profile of NSAIDs. Combinations of NSAIDs with gastroprotective agents, such as proton pump inhibitors, histamine-2-receptor antagonists, and prostaglandin analogues, have been shown to reduce GI AE event rates. Transdermal absorption of NSAIDs is a relatively new approach to reducing NSAID toxicity. Topical NSAID preparations include gels, creams, sprays, solutions, plasters, and bandages. In some studies, these have demonstrated comparable analgesic efficacy to traditional oral NSAIDs. Moreover, studies indicate that through reductions in bioavailability, topical NSAIDs may reduce the risk for CV, GI, and renal AEs. Topical NSAIDs have recently been included in updated guidelines for osteoarthritis. However, their long-term efficacy has not been extensively studied and remains uncertain.

Opioids

Institution of opioid therapy in patients refractory to NSAID and acetaminophen therapy with moderately severe to severe pain is the general consensus in a majority of the guidelines reviewed. However, opioid use is controversial due to the potential for misuse, abuse, and addiction, as well as the side effect profile. In 2008, 74% of all drug overdoses were related to an opioid. An estimated 739,000 persons ≥12 years of age were treated for narcotic analgesic abuse in 2009, and prescription opioid abuse increased 140% from 1992 to 2003. To curb misuse, physician–patient decision-making guidelines and tools, such as the FDA’s Risk Evaluation and Mitigation Strategy, for opioid medications have been developed. Furthermore, chronic opioid use is associated with the development of tolerance and hyperalgesia, which can reduce analgesic efficacy over time.

Tramadol, a weak opioid with agonistic norepinephrine and serotonin activity, exhibits a lower abuse and tolerance potential compared with traditional opioids, and may provide a safer therapeutic option for clinicians to prescribe. However, evidence of limited short- and long-term efficacy and an established side effect profile present additional barriers to the use of tramadol and other opioids.

The prevalence of nausea, constipation, dizziness, vomiting, and drowsiness has altered prescription practices, leading to the development of opioid-related side effects. In a 2007 meta-analysis by Avouac et al., 25% of patients discontinued opioid therapy due to toxicity. All opioids, including tramadol, only modestly improve functional impairment and the effectiveness of opioids in chronic therapy remains unclear.

Other agents

Acetaminophen, NSAIDs, and opioids are the most frequently prescribed drugs for the management of OA, but a number of other pharmacologic options have been recommended as well. Tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors (SNRIs) have been investigated for use in OA. Duloxetine is the only antidepressant currently approved by the FDA for the management of chronic musculoskeletal pain. The FDA recommendation was based on two randomized, double-blind, placebo-controlled comparison trials of duloxetine 60 mg and 120 mg in the management of OA. Over 13 weeks, these trials demonstrated that duloxetine administration promoted improvements in functional capacity and demonstrated analgesic efficacy. SNRIs are generally well tolerated; however, they are associated – albeit rarely – with hepatotoxicity and serotonin syndrome, a potentially lethal condition characterized by confusion, autonomic hyperactivity, and neuromuscular dysfunction. As such, therapy with duloxetine should be individualized to assess patient risk for AE development and be viewed as an effective adjunct to classic therapy. With the exception of the ACR guidelines, the current OA management guidelines were drafted prior to the release of these study results and the approval of duloxetine. Therefore, duloxetine’s presence in guidelines is
Multimodal therapy

Multimodal therapy, through the use of analgesic combinations, may prove valuable to OA management by enhancing pain relief and allowing for reductions in AE risk. It should be noted that, although the use of agents with complementary mechanisms of action provides clinical benefit, analgesic combinations also have the potential to cause additive, synergistic, or unexpected drug–drug interactions. Acetaminophen/NSAID combinations have been shown to provide better OA pain relief than either agent alone and at lower doses, but have an increased risk for GI events. Tramadol/acetaminophen combinations have proven effective in the management of OA and their use as an adjunct to NSAID therapy has demonstrated superior efficacy in alleviating OA pain and improving functional capacity compared with an NSAID alone. This suggests the potential to reduce NSAID dose while maintaining clinical efficacy. However, tramadol/acetaminophen has only been approved for short-term (<5 days) use in the management of acute pain.

Conclusion

Nearly half of the United States population will develop OA by 85 years of age. The public health and economic consequences of OA care are significant, and exploring the rationale driving pharmacologic management of OA is complex. Conservative management of OA is difficult and evidence-based guidelines provide clinicians with access to rigorously researched therapeutic strategies. However, these guidelines sometimes conflict and acetaminophen, NSAIDs, and opioids are plagued by efficacy and/or safety concerns, complicating clinician adherence to the guidelines. The substantial rate of treatment failure directly linked to these concerns has led to a significant unmet clinical need. Pain and persistent functional impairment can have a devastating impact on quality of life. These concerns highlight the need for novel pharmacologic options in the treatment of OA. The COX-2 enzyme remains an appropriate therapeutic target. In addition, advances in our understanding of the mechanisms of pain have helped identify other targets for OA pain management. For example, disease-modifying agents are currently in development. Multimodal therapy may provide more efficacious OA therapeutic options that overcome safety limitations. Pain and persistent functional impairment can have a devastating impact on quality of life. Positioned at the forefront of disease management, PCPs rely on advancing clinical science to drive decision making. Adoption of novel therapeutic options may simplify the complex interplay between drug tolerability, efficacy, and current treatment guidelines.

Transparency

Declaration of funding

Editorial support was sponsored by Iroko Pharmaceuticals LLC.

Declaration of financial/other relationships

B.M. is an advisor for Pfizer Inc., NeurogesX Inc., INSYS Therapeutics Inc., Teva Pharmaceutical Industries Ltd., Sucampo Pharmaceuticals Inc., and Zogenix Inc. P.T. has disclosed that she has no significant relationships with or financial interests in any commercial companies related to this study or article. The authors had full control in the development of this manuscript and did not receive honoraria.

CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed that they have no relevant financial relationships.

Acknowledgments

Editorial assistance was provided by Colville Brown, MD, of AlphaBioCom LLC.

References


545
26. Mann C, Gooberman-Hill R. Health care provision for osteoarthritis: concordance between what patients would like and what health professionals think they should have. Arthritis Care Res 2011;63:963-72
43. James LP, Mayeux PR, Hinson JA. Acetaminophen-induced hepatotoxicity. Drug Metab Dispos 2003;31:1499-506
48. Food and Drug Administration. FDA drug safety communication: prescription acetaminophen products to be limited to 325 mg per dosage unit; boxed warning will highlight potential for severe liver failure. 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm [Last accessed 17 May 2012]
52. Garcia Rodriguez LA, Hernandez-Diaz S. Relative risk of upper gastrointestinal events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. Am J Gastroenterol 2008;103:872-82


100. Kuehn BM. Serotonin syndrome update. JAMA 2011;306:2661


