CMRO

Current Medical Research & Opinion Vol. 29, No. 5, 2013, 539–548

0300-7995
doi:10.1185/03007995.2013.785391

Article RT-0012.R1/785391

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; rundrbillrun@cox.net

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

Accepted: 11 March 2013; published online: 2 April 2013
Citation: Curr Med Res Opin 2013; 29:539–48

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[1]. 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[1–3]. With approximately $89 billion spent annually, OA management is costly to the health care system[1].

OA is characterized by articular symptoms secondary to cartilage destruction and a subsequent tissue response[4]. Clinical manifestations of OA include,

but are not limited to, joint pain and stiffness resulting in functional impairment[5]. OA follows an intermittently progressive course with therapeutic strategies aimed at improving quality of life by actively addressing functional impairment and pain[6,7]. Disease-modifying agents are not currently available, limiting therapy to symptomatic treatment[8]. 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[9–11]. However, OA management is complicated by the limitations of the most commonly prescribed treatment options[9,10]. 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[12].

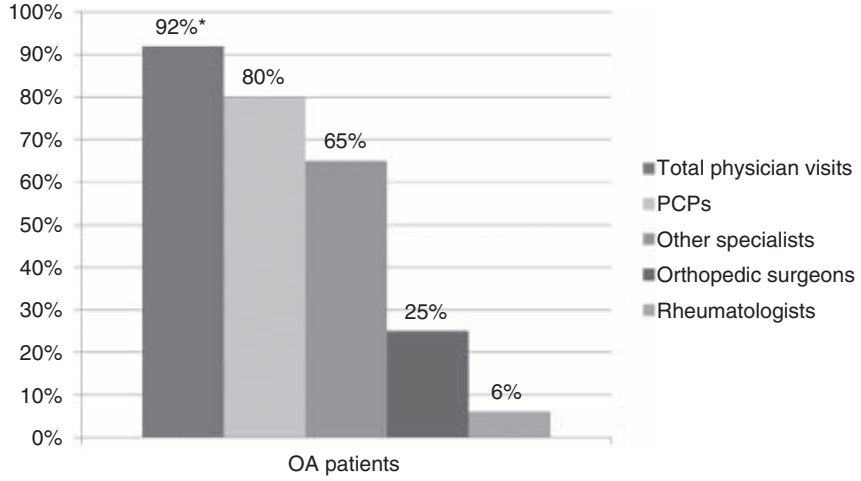
OA management is largely site specific. Destruction of the weight-bearing hip and knee joints can drastically reduce functional capacity and has the most significant clinical impact[13]. This review will focus on the clinical challenges of managing OA pain of the knee and hip with acetaminophen, NSAIDs, 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[1,14]. 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 (Figure 1)[15,16]. PCPs forge long-standing relationships with patients, allowing for an integrative approach to OA management[16,17]. However, ongoing management can be complex. Cartilage is weakly innervated, so radiographic findings consistent with OA may not present as clinically relevant symptoms[4]. 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[12]. 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.*[17], moderate or severe OA knee pain was associated with difficulty in the completion of all categories of the Health Assessment Questionnaire. Furthermore, the first National Health and Nutrition Examination Survey



*65% of patients also visited non-physicians.

Figure 1. US ambulatory clinic visits by specialty from 2002 to 2005. (Adapted with permission from Cisternas MG, Yelin E, Katz JN, et al. Ambulatory visit utilization in a national, population-based sample of adults with osteoarthritis. Arthritis Rheum 2009;61(12):1694–1703.)

(NHANES) demonstrated that baseline OA knee pain was associated with increased risk of developing functional impairment up to 13 years later[17,18].

It is apparent that OA management strategies are focused largely on clinical presentation. Symptom-based approaches prevent unnecessarily aggressive therapeutic regimens[18] and effective pain relief can have a direct and substantial impact on clinical outcomes[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[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[23]. Patients with arthritis who participated in the NHANES III survey (2001–2002) reported greater impairments in quality of life than patients with cancer[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[25].

The socioeconomic, psychological, and pathophysiological impact of OA pain is of considerable clinical concern[26]. Shifting prescription practices highlight widespread uncertainty, as well as dissatisfied clinicians and patients. A 2003 retrospective study by Gore *et al.*[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 *et al.*[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[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[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[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[31]. However, COX-2 inhibitors are linked to myocardial infarction (MI) and other serious cardiovascular (CV) events[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[31–33].

Fundamentally, the OA treatment paradigm stems from an emphasis on drug-related complications, exemplified by the controversy surrounding COX-2 inhibitors[12]. The elderly are especially susceptible to AEs associated with acetaminophen, NSAIDs, and opioids[25]. 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[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[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[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

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

Society (Year)	Recommendation
Acetaminophen	
EULAR (2005)[36]	First-line agent
NICE (2008)[37]	First-line agent
AAOS (2008)[38]	First-line agent
OARSI (2010)[39,40]	First-line agent in patients with mild-to-moderate OA pain
ACR (2012)[41]	First-line agent
Non-selective Oral NSAIDs	
AAOS (2008)[41]	First-line agent[a]
ACR (2012)[37]	Second-line agent in patients <75 years of age without a history of GI bleeding within the last year[a]
NICE (2008)[36]	Second-line agent that should be co-prescribed with a PPI
EULAR (2005)[38]	Second-line agent[a]
OARSI (2010)[39,40]	First-line agent in moderate-to-severe OA pain; second-line agent in mild-to-moderate OA pain[a]
Selective COX-2 Inhibitors	
AAOS (2008)[41]	First-line agent in patients with a history of PUD and GI bleeding or concurrent corticosteroid or anticoagulant use
ACR (2012)[37]	Second-line agent in patients with more than a 1-year history of symptomatic or complicated GI bleed or ulcer[b] and third-line agents in patients ≥75
NICE (2008)[36]	Second-line agent that should be co-prescribed with a PPI
EULAR (2005)[38]	Second-line agent in patients with increased risk for GI AEs
OARSI (2010)[39,40]	Second-line agent in patients with increased risk for GI AEs
Topical NSAIDs	
AAOS (2008)[41]	First-line agent in patients with a history of PUD and GI bleeding or concurrent corticosteroid or anticoagulant use
ACR (2012)[37]	Second-line agent in OA of the knee
NICE (2008)[36]	First-line agent
EULAR (2005)[38]	Demonstrate safety and clinical efficacy[c]
OARSI (2010)[39,40]	Adjunctive or alternative treatment to oral NSAIDs
Opioids	
AAOS (2008)[41]	No recommendation
ACR (2012)[37]	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
NICE (2008)[36]	Second-line agent
EULAR (2005)[38]	Management of disease refractory to, or inappropriate for, management with other agents
OARSI (2010)[39,40]	Management of disease refractory to, or inappropriate for, management with other agents
Duloxetine	
ACR (2012)[37]	Second-line agent in patients ≥75

[i]AAOS does not provide guidelines for managing OA of the hip.
[a]Use with gastroprotective agent in patients at increased risk for GI events.
[b]Use with proton pump inhibitor in patients with a history of GI bleed within the past year.
[c]No 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.

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 with uncontrolled pain on acetaminophen (Table 1)[36–41]. Additionally, the ACR suggests duloxetine administration in patients ≥75 years of age who have failed acetaminophen therapy[41].

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[36–41]. 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[20,25,42].

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[40,43]. 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[44,45]. However, 14% to 30% of acetaminophen-induced hepatoxicity 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[46,47].

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[48]. 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[40,49–51]. However, most generic acetaminophen products have not reduced the maximum daily dosage from 4 g/day[51].

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[52]. Furthermore, Rahme *et al.* observed elevated hospitalization rates for GI complications in patients receiving acetaminophen at >3 g/day[53].

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)[54]. 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[55]. 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[56] and a 1.20 RR in another[57].

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[58]. 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[59]. 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[60]. Oral NSAID-related GI complications alone comprise a significant percentage of all medication-related AEs[61]. 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[62]. These serious upper GI injuries account for 34% of all medication-related AEs and are responsible for 3200 deaths annually in the United States[63]. Co-administration of gastroprotective agents can reduce GI AE risk, a costly alternative that is not without persistent risk[64]. Oral NSAIDs are also associated with the development of serious disease of the small and large intestine, such as stricture, bleeding, and perforation[65].

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[66,67]. NSAIDs have been associated with MI, stroke, hypertension, exacerbation of chronic heart failure, and CV death[68]. 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[69]. 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[70]. 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[68]. 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[71]. 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[72]. NSAIDs are also associated with a diverse array of renal complications, including electrolyte abnormalities, fluid retention, nephrotic syndrome, interstitial nephritis, and renal papillary necrosis[73].

The FDA recommends the use of NSAIDs for the shortest duration consistent with patient treatment goals[60]; however, NSAID-related GI and CV AEs (and some renal AEs) can occur at any time following administration of NSAIDs[74–76]. 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[75]. A case-control study of 138,949 subjects supports these findings, indicating that both short- and long-term NSAID exposure is associated with MI[77]. Similarly, GI complications can develop within days following NSAID use and renal complications can occur within hours[74,76]. 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[25]. However, the efficacy of NSAIDs for potent pain relief in OA is well established[58]. 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[79–81]. Transdermal absorption of NSAIDs is a relatively new approach to reducing NSAID toxicity. Topical NSAID preparations include gels, creams, sprays, solutions, plasters, and bandages[82]. In some studies, these have demonstrated comparable analgesic efficacy to traditional oral NSAIDs[82–85]. Moreover, studies indicate that through reductions in bioavailability, topical NSAIDs may reduce the risk for CV, GI, and renal AEs[86]. Topical NSAIDs have recently been included in updated guidelines for osteoarthritis[36,37,39]. However, their long-term efficacy has not been extensively studied and remains uncertain[82].

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[36,38–41]. 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[87]. 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[88,89]. 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[19,90]. Furthermore, chronic opioid use is associated with the development of tolerance and hyperalgesia, which can reduce analgesic efficacy over time[91].

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[92]. 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, reducing opioid use[93,94]. Treatment failure is frequently coupled with 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[85]. All opioids, including tramadol, only modestly improve functional impairment and the effectiveness of opioids in chronic therapy remains unclear[93,94].

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[9,10,95,96]. Duloxetine is the only antidepressant currently approved by the FDA for the management of chronic musculoskeletal pain[37,97]. 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[9,10]. Over 13 weeks, these trials demonstrated that duloxetine administration promoted improvements in functional capacity and demonstrated analgesic efficacy[98]. 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[99–101]. 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

scarce, emphasizing the need for new, clinically relevant guidelines[37,98].

Topical agents, such as capsaicin and 5% lidocaine, have demonstrated efficacy in the management of OA[102–105]. In a 2008 comparison study, lidocaine 5% patch, a peripheral analgesic, provided similar pain relief compared with celecoxib 200 mg in patients with knee OA[105]. Capsaicin provides pain relief through reductions in nociceptive neurotransmitter levels and has been shown to effectively control OA pain and its adjunctive use is suggested in some OA guidlines[36–41,102,103]. The use of targeted topical therapy with capsaicin may reduce AEs by limiting systemic exposure and lidocaine provides physicians with an alternative to commonly used oral analgesics.

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[106]. 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[107,108]. 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[109–112]. 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[113].

Conclusion

Nearly half of the United States population will develop OA by 85 years of age[114]. 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[115,116]. In addition, advances in our understanding of the mechanisms of pain have helped identify other targets for OA pain management[117]. For example, disease-modifying agents are currently in development[118–120]. 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

1. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum 2008;58:26-35
2. Leigh JP, Seavey W, Leistikow B. Estimating the costs of job related arthritis. J Rheumatol 2001;28:1647-54
3. Sinusas K. Osteoarthritis: diagnosis and treatment. Am Fab Physician 2012;85:49-56
4. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039-49
5. Lubar D, White PH, Callahan LF, et al. A national public health agenda for osteoarthritis 2010. Semin Arthritis Rheum 2010;39:323-6
6. Hochberg MC. Prognosis of osteoarthritis. Ann Rheum Dis 1996;55:685-8
7. Hadler NM. Knee pain is the malady – not osteoarthritis. Ann Intern Med 1992;116:598-9

8. Hinton R, Moody RL, Davis AW, Thomas SF. Osteoarthritis: diagnosis and therapeutic considerations. Am Fam Physician 2002;65:841-8
9. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. Pain 2009;146:253-60
10. Chappell AS, Desaiah D, Liu-Seifert H, et al. A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee. Pain Pract 2011;11:33-41
11. Staiger TO, Gaster B, Sullivan MD, Deyo RA. Systematic review of antidepressants in the treatment of chronic low back pain. Spine 2003;28:2540-5
12. Rosemann T, Wensing M, Joest K, et al. Problems and needs for improving primary care of osteoarthritis patients: the views of patients, general practitioners and practice nurses. BMC Musculoskelet Disord 2006;7:48
13. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000;133:635-46
14. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol 2007;34:172-80
15. Cisternas MG, Yelin E, Katz JN, et al. Ambulatory visit utilization in a national, population-based sample of adults with osteoarthritis. Arthritis Rheum 2009;61:1694-703
16. Hootman JM, Helmick CG, Schappert SM. Magnitude and characteristics of arthritis and other rheumatic conditions on ambulatory medical care visits, United States, 1997. Arthritis Rheum 2002;47:571-81
17. Jordan J, Luta G, Renner J, et al. Knee pain and knee osteoarthritis severity in self-reported task specific disability: the Johnston County Osteoarthritis Project. J Rheum 1997;24:1344-9
18. Creamer P, Hochberg MC. Why does osteoarthritis of the knee hurt – sometimes? Br J Rheumatol 1997;36:726-8
19. Alford DP, Liebschutz J, Chen IA, et al. Update in pain medicine. J Gen Intern Med 2008;23:841-5
20. Carr DB, Goudas LC. Acute pain. Lancet 1999;353:2051-8
21. Nathan C. Points of control in inflammation. Nature 2002;420:846-52
22. Argoff CE. Recent developments in the treatment of osteoarthritis with NSAIDs. Curr Med Res Opin 2011;27:1315-27
23. Creamer P, Hochberg MC. The relationship between psychosocial variables and pain reporting in osteoarthritis of the knee. Arthritis Care Res 1998;11:60-5
24. Centers for Disease Control and Prevention. Health Related Quality of Life Surveillance – United States. Morb Mortal Wkly Rep 2005;54 (No. SS-4):22
25. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. American Geriatrics Society panel on the pharmacological management of persistent pain in older persons. Pain Med 2009;10:1062-83
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
27. Gore M, Sadosky AB, Leslie DL, et al. Therapy switching, augmentation, and discontinuation in patients with osteoarthritis and chronic low back pain. Pain Pract 2012;12:457-68
28. Walker AM, Chan KW, Yood RA. Patterns of interchange in the dispensing of non-steroidal anti-inflammatory drugs. J Clin Epidemiol 1992;45:187-95
29. White AG, Birnbaum HG, Janagap C, et al. Direct and indirect costs of pain therapy for osteoarthritis in an insured population in the United States. J Occup Environ Med 2008;50:998-1005
30. Arellano FM, Yood MU, Wentworth CE, et al. Use of cyclo-oxygenase 2 inhibitors (COX-2) and prescription non-steroidal anti-inflammatory drugs (NSAIDS) in UK and USA populations. Implications for COX-2 cardiovascular profile. Pharmacoepidemiol Drug Saf 2006;15:861-72
31. Dai C, Stafford RS, Alexander GC. National trends in cyclooxygenase-2 inhibitor use since market release: nonselective diffusion of a selectively cost-effective innovation. Arch Intern Med 2005;165:171-7
32. Bansal SS, Joshi A, Bansal AK. New dosage formulations for targeted delivery of cyclo-oxygenase-2 inhibitors: focus on use in the elderly. Drugs Aging 2007;24:441-51
33. Greenberg JD, Fisher MC, Kremer J, et al. The COX-2 inhibitor market withdrawals and prescribing patterns by rheumatologists in patients with gastrointestinal and cardiovascular risk. Clin Exp Rheumatol 2009;27:395-401
34. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342:1317-22
35. Shekelle PG, Ortiz E, Rhodes S, et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? JAMA 2001;286:1461-7
36. Zhang W, Doherty M, Arden N, et al. EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64:669-81
37. Conaghan PG, Dickson J, Grant RL. Guideline development. Care and management of osteoarthritis in adults: summary of NICE guidance. BMJ 2008;336:502-3
38. American Academy of Orthopaedic Surgeons. Treatment of Osteoarthritis of the Knee (non-arthroplasy). Rosemont, IL: American Academy of Orthopaedic Surgeons, 2008
39. Zhang W, Moskowitz RW, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, part II: OARSI evidence-based, expert consensus guidelines. Osteoarthr Cartil 2008;16:137-62
40. Zhang W, Nuki G, Moskowitz RW, et al. OARSI recommendations for the management of hip and knee osteoarthritis: part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthr Cartil 2010;18:476-99
41. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64:455-74
42. Gordon DB, Dahl JL, Miaskowski C, et al. American Pain Society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Arch Intern Med 2005;165:1574-80
43. James LP, Mayeux PR, Hinson JA. Acetaminophen-induced hepatotoxicity. Drug Metab Dispos 2003;31:1499-506
44. Nourjah P, Ahmad SR, Karwoski C, Willy M. Estimates of acetaminophen (paracetamol)-associated overdoses in the United States. Pharmacoepidemiol Drug Saf 2006;15:398-405
45. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. Lancet 2010;376:190-201
46. Gyamlani GG, Parikh CR. Acetaminophen toxicity: suicidal vs. accidental. Crit Care 2002;6:155-9
47. Schiødt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. New Engl J Med 1997;337:1112-18
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]
49. Winn PA, Dentino AN. Effective pain management in the long-term care setting. J Am Med Dir Assoc 2004;5:342-52
50. Healthcare MC. New initiative to help encourage appropriate use of acetaminophen. 2011. Available at: http://www.tylenol.com/page2.jhtml?id=tylenol/news/newdosing.inc [Last accessed 18 February 2013]
51. Krenzelok EP, Royal MA. Confusion: acetaminophen dosing changes based on NO evidence in adults. Drugs in R&D 2012;12:45-8
52. Garcia Rodriguez LA, Hernandez-Diaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. Epidemiology 2001;12:570-6
53. Rahme E, Barkun A, Nedjar H, et al. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. Am J Gastroenterol 2008;103:872-82

54. Chan AT, Manson JE, Albert CM, et al. Nonsteroidal antiinflammatory drugs, acetaminophen, and the risk of cardiovascular events. Circulation 2006;113:1578-87
55. Forman JP, Rimm EB, Curhan G. Frequency of analgesic use and risk of hypertension among men. Arch Intern Med 2007;167:394-9
56. Curhan GC, Willett WC, Rosner B, Stampfer MJ. Frequency of analgesic use and risk of hypertension in younger women. Arch Intern Med 2002;162: 2204-8
57. Dedier J, Stampfer MJ, Hankinson SE, et al. Nonnarcotic analgesic use and the risk of hypertension in US women. Hypertension 2002;40:604-8; discussion 601-3
58. Towheed TE, Maxwell L, Judd MG et al. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006(1):CD004257
59. Hunt RH, Choquette D, Craig BN, et al. Approach to managing musculoskeletal pain: acetaminophen, cyclooxygenase-2 inhibitors, or traditional NSAIDs? Can Fam Physician 2007;53:1177-84
60. Food and Drug Administration. Public Health Advisory – FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm [Last accessed 7 April 2005]
61. Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of analgesics in older adults with arthritis. Arch Intern Med 2010;170:1968-76
62. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med 2000;160:2093-9
63. Tarone RE, Blot WJ, McLaughlin JK. Nonselective nonaspirin nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding: relative and absolute risk estimates from recent epidemiologic studies. Am J Ther 2004;11: 17-25
64. Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. Health Technol Assess 2007;11:iii-iv, 1-164
65. Lanas A. A review of the gastrointestinal safety data – a gastroenterologist's perspective. Rheumatology 2010;49(Suppl 2):ii3-10
66. Gislason GH, Jacobsen S, Rasmussen JN, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. Circulation 2006;113:2906-13
67. McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. PLoS Med 2011;8:e1001098
68. Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. BMJ 2011;342:c7086
69. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case–control study. Lancet 2005;365:475-81
70. Bak S, Andersen M, Tsiropoulos I, et al. Risk of stroke associated with nonsteroidal anti-inflammatory drugs: a nested case–control study. Stroke 2003;34:379-86
71. Schneider V, Levesque LE, Zhang B, et al. Association of selective and conventional nonsteroidal anti-inflammatory drugs with acute renal failure: a population-based, nested case–control analysis. Am J Epidemiol 2006; 164:881-9
72. Gooch K, Culleton BF, Manns BJ, et al. NSAID use and progression of chronic kidney disease. Am J Med 2007;120:280:e281-7
73. Whelton A. Renal aspects of treatment with conventional nonsteroidal anti-inflammatory drugs versus cyclooxygenase-2-specific inhibitors. Am J Med 2001;110(Suppl 3A):33-42S
74. Richy F, Bruyere O, Ethgen O, et al. Time dependent risk of gastrointestinal complications induced by non-steroidal anti-inflammatory drug use: a consensus statement using a meta-analytic approach. Ann Rheum Dis 2004;63:759-66
75. Schjerning Olsen A-M, Fosbøl EL, Lindhardsen J, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction/clinical perspective. Circulation 2011;123:2226-35
76. Brater DC. Anti-inflammatory agents and renal function. Semin Arthritis Rheum 2002;32(3 Suppl 1):33-42
77. Helin-Salmivaara A, Virtanen A, Vesalainen R, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case–control study from Finland. Eur Heart J 2006;27:1657-63
78. US Food and Drug Administration. Public Health Advisory: FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). 2005. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm150314.htm [Last accessed 5 March 2012]
79. Gigante A, Tagarro I. Non-steroidal anti-inflammatory drugs and gastroprotection with proton pump inhibitors: a focus on ketoprofen/omeprazole. Clin Drug Investig 2012;32:221-33
80. Hochberg MC, Fort JG, Svensson O, et al. Fixed-dose combination of enteric-coated naproxen and immediate-release esomeprazole has comparable efficacy to celecoxib for knee osteoarthritis: two randomized trials. Curr Med Res Opin 2011;27:1243-53
81. Laine L, Kivitz AJ, Bello AE, et al. Double-blind randomized trials of single-tablet ibuprofen/high-dose famotidine vs. ibuprofen alone for reduction of gastric and duodenal ulcers. Am J Gastroenterol 2012;107:379-86
82. Arnstein PM. Evolution of topical NSAIDs in the guidelines for treatment of osteoarthritis in elderly patients. Drugs Aging 2012;29:523-31
83. Tugwell PS, Wells GA, Shainhouse JZ. Equivalence study of a topical diclofenac solution (Pennsaid) compared with oral diclofenac in symptomatic treatment of osteoarthritis of the knee: a randomized controlled trial. J Rheumatol 2004;31:2002-12
84. Friedman PM, Mafong EA, Friedman ES, Geronemus RG. Topical anesthetics update: EMLA and beyond. Dermatol Surg 2001;27:1019-26
85. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2007;15:957-65
86. Makris UE, Kohler MJ, Fraenkel L. Adverse effects of topical nonsteroidal antiinflammatory drugs in older adults with osteoarthritis: a systematic literature review. J Rheumatol 2010;37:1236-43
87. Centers for Disease Control and Prevention. Vital signs: overdoses of prescription opioid pain relievers – United States, 1999–2008. MMWR Morb Mortal Wkly Rep 2011;60:1487-92
88. Bollinger L. Under the Counter: The Diversion of Abuse of Controlled Prescription Drugs in the U.S. New York: Columbia University, 2005
89. McCarberg BH. Pain management in primary care: strategies to mitigate opioid misuse, abuse, and diversion. Postgrad Med 2011;123:119-30
90. Cicero TJ, Inciardi JA, Munoz A. Trends in abuse of oxycontin and other opioid analgesics in the United States: 2002–2004. J Pain 2005;6:662-72
91. Chu LF, Clark DJ, Angst MS. Opioid tolerance and hyperalgesia in chronic pain patients after one month of oral morphine therapy: a preliminary prospective study. J Pain 2006;7:43-8
92. Altman RD. Practical considerations for the pharmacologic management of osteoarthritis. Am J Manag Care 2009;15(8 Suppl):S236-43
93. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006;174:1589-94
94. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. Osteoarthr Cartil 2007;15:957-65
95. Scott WA. The relief of pain with an antidepressant in arthritis. Practitioner 1969;202:802-7
96. Sullivan M, Bentley S, Fan MY, Gardner G. A single-blind placebo run-in study of venlafaxine XR for activity-limiting osteoarthritis pain. Pain Med 2009;10:806-12

97. Food and Drug Administration. FDA clears Cymbalta to treat chronic musculoskeletal pain. 2010. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm232708.htm [Last accessed 23 July 2012]
98. Hochberg MC, Wohlreich M, Gaynor P, et al. Clinically relevant outcomes based on analysis of pooled data from 2 trials of duloxetine in patients with knee osteoarthritis. J Rheumatol 2012;39:352-8
99. Boyer EW, Shannon M. The serotonin syndrome. New Engl J Med 2005;352:1112-20
100. Kuehn BM. Serotonin syndrome update. JAMA 2011;306:2661
101. Vuppalanchi R, Hayashi PH, Chalasani N, et al. Duloxetine hepatotoxicity: a case-series from the drug-induced liver injury network. Aliment Pharmacol Ther 2010;32:1174-83
102. Kosuwon W, Sirichatiwapee W, Wisanuyotin T, et al. Efficacy of symptomatic control of knee osteoarthritis with 0.0125% of capsaicin versus placebo. J Med Assoc Thai 2010;93:1188
103. Chou R, McDonagh M, Nakamoto E, Griffin J. Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review. Rockville (MD): Agency for Healthcare Research and Quality (US), 2011
104. Gammaitoni AR, Galer BS, Onawola R, et al. Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: results of a pilot 2-week, open-label study using the neuropathic pain scale. CMRO 2004;20(S2):13-19
105. Kivitz A, Fairfax M, Sheldon EA, et al. Comparison of the effectiveness and tolerability of lidocaine patch 5% versus celecoxib for osteoarthritis-related knee pain: post hoc analysis of a 12 week, prospective, randomized, active-controlled, open-label, parallel-group trial in adults. Clin Ther 2008;30:2366
106. Raffa RB. Pharmacology of oral combination analgesics: rational therapy for pain. J Clin Pharm Ther 2001;26:257-64
107. Buescher JJ, Meadows S, Saseen J. Do acetaminophen and a NSAID combined relieve osteoarthritis pain better than either alone? J Fam Pract 2004;53:501-3
108. Ong CKS, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 2010;110:1170-9
109. Rosenthal NR, Silverfield JC, Wu S-C, et al, on behalf of the CAPSS-105 Study Group. Tramadol/acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly patient population. J Am Geriatr Soc 2004;52:374-80
110. Cepeda MS, Camargo F, Zea C, Valencia L. Tramadol for osteoarthritis. Cochrane Database Syst Rev 2006(3):CD005522
111. Park K-S, Choi J-J, Kim W-U, et al. The efficacy of tramadol/acetaminophen combination tablets (Ultracet®) as add-on and maintenance therapy in knee osteoarthritis pain inadequately controlled by nonsteroidal anti-inflammatory drug (NSAID). Clin Rheumatol 2012;31:317-23
112. Emkey R, Rosenthal N, Wu S-C, et al. CAPSS-114 Study Group. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. J Rheumatol 2004;31:150-6
113. Ultracet (tramadol hydrochloride/acetaminophen tablets) Full Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, 2011
114. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. Arthritis Rheum 2008;59:1207-13
115. Amin AR, Attur M, Patel RN, et al. Superinduction of cyclooxygenase-2 activity in human osteoarthritis-affected cartilage. Influence of nitric oxide. J Clin Investig 1997;15;99:1231-7
116. Wolfe F, Zhao S, Lane N. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients: A survey of 1799 patients with osteoarthritis, rheumatoid arthritis, and fibromyalgia. Arthritis Rheum 2000;43:378-85
117. Dray A, Read S. Arthritis and pain. Future targets to control osteoarthritis pain. Arthritis Res Ther 2007;9:212
118. Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. Age Ageing 2012;41:646-52
119. McAlindon TE, Driban JB, Lo GH. Osteoarthritis year 2011 in review: clinical. Osteoarthr Cartil 2012;20:197-200
120. Nagashima H, Suzuki M, Araki S, et al. Preliminary assessment of the safety and efficacy of tanezumab in Japanese patients with moderate to severe osteoarthritis of the knee: a randomized, double-blind, dose-escalation, placebo-controlled study. Osteoarthr Cartil 2011;19:1405-12

