

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,500

Open access books available

135,000

International authors and editors

165M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Long-Term Treatment of Osteoarthritis Pain: Achieving a Balance Between Efficacy and Tolerability for a Successful Chronic Therapy

Mila Etropolski

*Johnson & Johnson Pharmaceutical Research & Development, L.L.C.  
USA*

## 1. Introduction

Throughout the world, in both developed and developing countries, arthritis is one of the most common causes of chronic pain (Catala et al., 2002; Elliott et al., 1999; Johannes et al., 2010; Tsang et al., 2008). The National Arthritis Data Workgroup estimates that 46.4 million adults in the United States have been diagnosed with some form of arthritis based on analyses of data from the third National Health and Nutrition Examination Survey (NHANES III; 1991-1994), the 2003 to 2005 National Health Interview Survey, and 2005 US Census Bureau population estimates (Helmick et al., 2008; Lawrence et al., 2008). Within this group, approximately 27 million adults have been diagnosed with osteoarthritis, making it the most common form of arthritis in the United States (Lawrence et al., 2008).

The prevalence of osteoarthritis increases with age (Kopec et al., 2007; Lawrence et al., 2008; Sakalauskiene & Jauniskiene, 2010; Shane & Loeser, 2010). Based on data from approximately 4 million patients seen over a 1-year period in British Columbia, Canada, the estimated prevalence of osteoarthritis increases from approximately 7% in patients between 40 and 44 years of age to 26% in patients between 60 and 64 years of age and to 49% in patients between 80 and 84 years of age (Kopec et al., 2007). The prevalence of knee osteoarthritis is particularly high in the elderly, and knee osteoarthritis is a major cause of disability in elderly patients (Shane & Loeser, 2010). Based on data from NHANES III and the Framingham Osteoarthritis Study, the prevalence of knee osteoarthritis in the United States is estimated to be 14% in adults 26 years of age or older, 19% in those 45 years of age or older, 37% in those 60 years of age or older, and 44% in those over 80 years of age (Dillon et al., 2006; Felson et al., 1987; Lawrence et al., 2008).

Osteoarthritis can have a negative impact on health-related quality of life and psychological well-being (Axford et al., 2008; Breedveld, 2004; de Bock et al., 1995; Jinks et al., 2007; Majani et al., 2005; Salaffi et al., 2005). Patients with osteoarthritis are often limited in their ability to participate in main daily activities (eg, household duties, employment, body care, ambulation, and sleep) and to maintain their independence (de Bock et al., 1995; Hunter et al., 2008; Jinks et al., 2007; Segal et al., 2004). Patients' mental health has been shown to decrease progressively over time, and patients with more severe osteoarthritis pain are most likely to experience depression and to have difficulty coping with their disease (Axford et

al., 2008). In addition, patients with osteoarthritis have an increased risk of developing metabolic syndrome and cardiovascular disease (Breedveld, 2004; Puenpatom & Victor, 2009).

Osteoarthritis is also associated with a substantial economic cost (Kotlarz et al., 2009; Wagner, 2011; White et al., 2007). According to an analysis of a medical claims database of 32,043 privately insured patients from 1999 to 2004, the average annual direct cost of osteoarthritis was \$11,543 per patient, including \$8,602 in direct medical costs and \$2,941 in drug costs (White et al., 2007). Based on results of the data from the Medical Expenditure Panel Survey, which was conducted over a 10-year period from 1996 to 2005, osteoarthritis was estimated to have increased aggregate annual healthcare expenditures by \$185.5 billion per year (in 2007 dollars; Kotlarz et al., 2009).

Osteoarthritis can occur in any joint; however, it occurs most frequently in the knees, hips, and hands. Other commonly affected joints include those in the feet and the cervical or lumbar regions of the spine (Martel-Pelletier & Pelletier, 2010). Osteoarthritis is characterized by progressive degeneration of articular cartilage, bone remodeling and sclerosis, formation of osteophytes, synovial hypertrophy, and meniscal damage (Abramson & Attur, 2009; Felson, 2009; Hunter & Felson, 2006). The loss of articular cartilage, which is generally recognized as a defining characteristic of osteoarthritis, results from an imbalance in the dynamic equilibrium between the synthesis and degradation of the cartilaginous extracellular matrix (Abramson & Attur, 2009; Hinton et al., 2002; Michael et al., 2010). In normal articular cartilage, chondrocytes are responsible for the production and maintenance of the cartilaginous extracellular matrix; chondrocytes also act as mechano- and osmo-sensors, altering the rate of matrix synthesis or degradation in response to local physiochemical changes (Loeser, 2008; Martel-Pelletier & Pelletier, 2010; Shane & Loeser, 2010). However, in osteoarthritis, inflammatory and catabolic signals stimulate chondrocytes to synthesize proteolytic enzymes that actively degrade the articular cartilage matrix (Abramson & Attur, 2009; Shane & Loeser, 2010). In response to this increased degradation of cartilage matrix, chondrocytes trigger increased synthesis of the proteoglycan components of the matrix, but these newly synthesized proteoglycans are structurally altered and may have a reduced capacity to form new cartilage (Martel-Pelletier & Pelletier, 2010; Rizkalla et al., 1992). As osteoarthritis progresses, eventually chondrocytes are unable to synthesize enough proteoglycans to offset the degradation of the cartilage matrix. Irreversible matrix degradation and cartilage loss is followed by the development of synovitis, joint incongruence, and formation of subchondral cysts (Martel-Pelletier & Pelletier, 2010; Michael et al., 2010).

Although the loss of articular cartilage is considered to be the physiological hallmark of osteoarthritis, the destruction of cartilage is not directly responsible for the joint pain that is considered to be the clinical hallmark of the disease (Felson, 2009). The most likely sources of osteoarthritis pain are the bone, muscle, ligaments, periosteum, and synovium of the affected joints. Bone-related changes associated with osteoarthritis joint pain may include bone marrow lesions, sub-articular bone attrition, periostitis associated with osteophyte formation, subchondral microfractures, and bone angina. Osteoarthritis joint pain has also been linked to synovitis and joint effusions. In cases where osteoarthritis is secondary to joint injury with rupture of the ligaments, the nerves themselves may be a source of pain. Nerve fiber regrowth is typically abnormal and disorganized, comparable to that observed in animal models of nerve injury (Felson, 2009; Hunter et al., 2008).

Pain is usually the predominant symptom of osteoarthritis. Osteoarthritis pain is often described as deep and aching and is typically exacerbated by physical activity and relieved by rest. In advanced osteoarthritis, pain may become more constant and patients may experience pain while at rest, resulting in sleep disturbances that can further exacerbate pain (Hunter et al., 2008). Traditionally, osteoarthritis pain has been attributed to local tissue injury, which causes mechanical nociceptive pain (Gwilym et al., 2009; Hochman et al., 2010). However, results from several studies indicate that central sensitization (ie, increased response to stimulation mediated by amplification of signaling in the central nervous system) may also play a role in the pathophysiology of chronic osteoarthritis pain (Arendt-Nielsen et al., 2010; Courtney et al., 2010; Hochman et al., 2010; Kidd et al., 2007; Kosek & Ordeberg, 2000). In patients with chronic osteoarthritis, persistent joint damage, synovial inflammation, and subchondral bone changes are associated with chronic nociceptor stimulation. This stimulation can alter the mechanisms of nociceptive processing, resulting in modification of central pain-transmitting neurons and enhanced pain response (Arendt-Nielsen et al., 2010; Courtney et al., 2010; Hochman et al., 2010). Symptoms associated with central sensitization in patients with osteoarthritis include hypersensitivity to pain, skin sensitivity, and the spread of pain from the affected joint to large body areas (ie, referred pain; Arendt-Nielsen et al., 2010; Hochman et al., 2010; Hunter et al., 2008; Woolf, 2011).

## **2. Osteoarthritis management**

There are currently no treatment options available for osteoarthritis that prevent or reverse disease progression or deterioration of the affected joints (Felson, 2006, 2009; Hinton et al., 2002; Michael et al., 2010). For that reason, osteoarthritis treatment strategies are generally targeted toward alleviating the painful symptoms of osteoarthritis, improving patient function and quality of life, and slowing disease progression (Felson, 2006, 2009; Hinton et al., 2002; Hunter & Felson, 2006; Michael et al., 2010). A combination of nonpharmacologic and pharmacologic measures is recommended for the management of osteoarthritis (Zhang et al., 2008). If these treatment options fail to provide adequate pain relief and functional improvement, then partial or total joint replacement surgery is considered (Michael et al., 2010; Zhang et al., 2008).

### **2.1 Nonpharmacologic measures**

The most common nonpharmacologic measures used for the management of osteoarthritis pain are weight-loss and exercise programs (Jordan et al., 2003; Michael et al., 2010; Zhang et al., 2008). Some patients with osteoarthritis pain may also benefit from physical therapy, the use of mobility or orthopedic aids (eg, canes, crutches, wheeled walkers, knee braces, wedged shoe insoles), heat or cold therapy, transcutaneous electrical nerve stimulation, or acupuncture (American College of Rheumatology, 2000; Barron & Rubin, 2007; McHughes & Lipman, 2006; Zhang et al., 2008).

Obesity has been associated with an increased risk of development and progression of knee osteoarthritis and with an increased risk of falls; therefore, weight loss has been recommended to reduce pain and improve physical function and health status in patients with osteoarthritis (Felson et al., 2000; Klusmann et al., 2010; Messier, 2008). In a randomized controlled trial in overweight and obese patients with knee osteoarthritis who were 60 years of age or older (n = 252), modest weight loss due to changes in diet and

exercise habits was associated with significant improvements in physical functioning and mobility (Messier et al., 2004). In a meta-analysis of changes in pain and physical function experienced by patients with osteoarthritis who lost weight ( $n = 454$ ), Christensen and colleagues found that physical disability was significantly reduced in patients who lost more than 5.1% of their body weight at a rate of more than 0.24% per week (Christensen et al., 2007).

Current osteoarthritis treatment guidelines recommend that all patients participate in regular aerobic and muscle-strengthening exercise programs, which are intended to improve pain control, balance, strength, flexibility, and endurance (American College of Rheumatology, 2000; Coleman et al., 2010; Jordan et al., 2003; Zhang et al., 2008). The Physical Activity Guidelines Advisory Committee to the US Department of Health and Human Services found that there is strong evidence that moderate exercise, such as walking, can provide small to moderate improvements in pain relief and small improvements in function and disability in patients with osteoarthritis. These guidelines also state that patients with osteoarthritis can expect “significant improvements in pain, physical function, quality of life, and mental health” along with “delayed onset of disability” by engaging in low-impact physical activity 3 to 5 times per week for 30 to 60 minutes per session (Physical Activity Guidelines Advisory Committee, 2008). However, a recent systematic review of clinical trials of exercise therapy for managing hip osteoarthritis found little evidence that exercise therapy was effective for reducing osteoarthritis pain or improving joint function or quality of life (McNair et al., 2009). While the available evidence indicates that exercise can be beneficial for patients with knee osteoarthritis, the number of studies sufficiently powered to examine the effects of exercise on hip osteoarthritis is limited, and well-designed trials to determine joint-specific exercise recommendations are needed (McNair et al., 2009; Petrella, 2000).

## **2.2 Pharmacologic measures**

Pharmacologic options for the management of osteoarthritis pain include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular injections of hyaluronic acid or corticosteroids, the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine, and opioids (Zhang et al., 2008). In addition, some nutritional supplements have shown efficacy in the reduction of osteoarthritis-related pain and may slow disease progression (Gregory et al., 2008; McAlindon et al., 2000). Topical capsaicin or lidocaine may also be used as adjunctive therapy for pain relief in combination with other therapies (Barron & Rubin, 2007; Jordan et al., 2003; Zhang et al., 2008).

### **2.2.1 Dietary supplements**

A number of dietary supplements have been marketed for the management of osteoarthritis (Gregory et al., 2008). Supplements containing glucosamine sulfate, chondroitin sulfate, and/or *S*-adenosylmethionine may provide pain relief and functional improvement in patients with osteoarthritis, and these supplements may have structure-modifying effects that may slow disease progression. However, results from clinical studies of these supplements have been mixed (Gregory et al., 2008; McAlindon et al., 2000; Zhang et al., 2008; Zhang et al., 2010).

Glucosamine is a naturally occurring constituent of cartilage proteoglycans found in ligaments, synovial fluid, and other joint structures. In a pooled analysis of 20 randomized

controlled trials in patients with knee osteoarthritis ( $n = 2,570$ ), treatment with glucosamine was associated with a 28% improvement in pain and a 21% improvement in function using the Lequesne index. However, 5 of the 20 studies analyzed failed to show that glucosamine was superior to placebo (Towheed et al., 2005; Towheed & Anastassiades, 2007). The inconsistency of results from different trials of glucosamine may be due to the use of different products (ie, glucosamine sulfate vs glucosamine hydrochloride), different trial designs, and different analysis methods (Gregory et al., 2008; McAlindon et al., 2000). In 2 separate 3-year, randomized placebo-controlled trials of glucosamine sulfate (1,500 mg/day) in patients with knee osteoarthritis, patients who received glucosamine sulfate had no significant average change in joint-space width, while patients who received placebo had significant joint-space narrowing (Pavelka et al., 2002; Reginster et al., 2001). These results suggest that glucosamine sulfate may slow the progression of osteoarthritis in patients with mild to moderate disease (Zhang et al., 2008).

Chondroitin sulfate is a glycosaminoglycan involved in the formation of cartilage and other joint matrix structures. Evidence supporting the clinical benefits of chondroitin sulfate for the improvement of osteoarthritis symptoms is inconsistent (Reichenbach et al., 2007). In a recent meta-analysis of 10 large-scale placebo-controlled trials of chondroitin, glucosamine, or their combination ( $n = 3,803$ ), Wandel and colleagues found that none of these therapies were associated with significant improvements in pain, as measured on a 10-cm visual analog scale, nor were they associated with any significant reduction in joint-space narrowing compared with placebo (Wandel et al., 2010).

S-Adenosylmethionine is a naturally occurring molecule involved in several different metabolic pathways. S-Adenosylmethionine may increase chondrocyte production and cartilage thickness and may decrease cytokine-induced chondrocyte damage, thus slowing the progression of osteoarthritis (Gregory et al., 2008). Results of clinical trials of S-adenosylmethionine have been consistently positive, showing that the efficacy of S-adenosylmethionine is superior to that of placebo and similar to that of NSAIDs; however, S-adenosylmethionine has a slower onset of action compared with NSAIDs (Hardy et al., 2003; Kim et al., 2009; Najm et al., 2004; Sander, 2003). S-Adenosylmethionine has a short shelf-life and may become unstable over time, and dose-escalation may be required to maintain efficacy (McHughes & Lipman, 2006). For these reasons and because no studies have been conducted comparing the risk/benefit ratio of S-adenosylmethionine with conventional therapies, current treatment guidelines do not recommend the use of S-adenosylmethionine for the management of osteoarthritis (Gregory et al., 2008; McHughes & Lipman, 2006).

### 2.2.2 Acetaminophen

Acetaminophen (up to 4 g/day) is recommended as the first-line oral analgesic therapy for the management of mild to moderate osteoarthritis pain (Altman, 2009; American College of Rheumatology, 2000; Jordan et al., 2003; Zhang et al., 2008). It can be used for the long-term management of osteoarthritis pain either alone or in combination with another analgesic (Jordan et al., 2003; Zhang et al., 2008).

The analgesic activity of acetaminophen is not fully understood, but is generally thought to result from the effects of acetaminophen on mediators of pain and inflammation in the central nervous system, possibly through interactions with nitric oxide, substance P receptors, or beta-endorphin. The anti-inflammatory properties of acetaminophen may block some of the inflammatory mechanisms involved in osteoarthritis pain (Flood, 2010).

In general, results from the published literature indicate that at standard recommended doses, pain relief achieved with acetaminophen is inferior to that achieved with most common NSAIDs (Boureau et al., 2004; Golden et al., 2004; Lee et al., 2004; Zhang et al., 2004); however, NSAIDs are associated with more severe side effects, especially when used at high doses for prolonged periods of time (Flood, 2010). A meta-analysis of data from 6 randomized placebo-controlled trials found that acetaminophen was safe and effective for the management of osteoarthritis pain; however, pain relief, clinical response rates, and health status were better with NSAIDs (including ibuprofen, diclofenac, rofecoxib, celecoxib, and naproxen) than with acetaminophen, and more patients preferred NSAIDs over acetaminophen. This meta-analysis also showed that the tolerability profile of acetaminophen was comparable to that of placebo, but NSAIDs were associated with more gastrointestinal side effects than acetaminophen or placebo (Zhang et al., 2004).

It should also be noted that although most studies of acetaminophen for the management of osteoarthritis pain have found that acetaminophen is associated with a low rate of adverse events (AEs; Flood, 2010), some studies have found associations between acetaminophen use and increased risks of upper gastrointestinal complications (Garcia Rodriguez & Hernandez-Diaz, 2001; Rahme et al., 2002) and renal toxicity (Fored et al., 2001). To date, these results are considered equivocal and have not resulted in changes to the recommendation that acetaminophen be used as first-line therapy for osteoarthritis pain management (Zhang et al., 2008).

### 2.2.3 NSAIDs

NSAIDs are recommended as a second-line treatment option in patients for whom acetaminophen treatment has failed to provide adequate pain relief (Jordan et al., 2003; Zhang et al., 2008). NSAIDs should be used at the lowest effective dose to avoid the risk of gastrointestinal and cardiovascular AEs, and long-term use should be avoided if possible (Zhang et al., 2008). In the United States, all marketed prescription NSAIDs carry a boxed warning about their potential to cause cardiovascular and gastrointestinal side effects (US Food and Drug Administration, 2005; Zhang et al., 2008).

NSAIDs are widely prescribed and are generally considered to be effective for the management of mild to moderate osteoarthritis pain. However, NSAIDs have a ceiling dose above which no additional analgesia can be achieved, which may limit their efficacy for the treatment of more severe pain (Fendrick & Greenberg, 2009). In a meta-analysis of the analgesic efficacy of NSAIDs for the short-term management of knee osteoarthritis pain (n = 10,845), Bjordal and colleagues observed that on average, NSAIDs reduced pain intensity by 10.1 mm (95% confidence interval [CI], 7.4-12.8) on a 10-cm visual analog scale, which was 15.6% better than placebo. Using a random-effects model, the authors determined that the effect size for pain reduction associated with NSAIDs was 0.32 (95% CI, 0.24-0.39; Bjordal et al., 2004).

Most common NSAIDs reduce inflammation through inhibition of the cyclo-oxygenase (COX) enzymes COX-1 and COX-2. COX-1 is expressed constitutively in many tissues and cells and may be involved in a number of physiologic functions, including protection of the gastrointestinal tract from its own acidity, platelet aggregation, and regulation of renal blood flow. In contrast, COX-2 is an inducible protein that is upregulated during inflammation and is primarily localized in inflamed tissue; COX-2 is not present in the stomach or small intestine (Crofford, 1997; Pham & Hirschberg, 2005). NSAIDs that inhibit

both COX-1 and COX-2 are classified as nonselective NSAIDs (eg, ibuprofen, diclofenac, naproxen, nabumetone, indomethacin, aspirin, etc.), whereas NSAIDs that selectively inhibit COX-2 are classified as selective COX-2 inhibitors or coxibs (eg, celecoxib, etoricoxib; Altman, 2009).

The analgesic effects of NSAIDs are predominantly attributed to the inhibition of COX-2, while the gastrointestinal side effects are thought to be caused by inhibition of COX-1 (Fendrick & Greenberg, 2009). Thus, nonselective NSAIDs are associated with an increased risk of severe upper gastrointestinal complications, including gastrointestinal tract bleeding, peptic ulcer disease, obstruction, and perforation (Pham & Hirschberg, 2005). It is estimated that chronic use of nonselective NSAIDs increases a patient's risk of upper gastrointestinal complications by 3- to 5-fold compared with patients who do not take nonselective NSAIDs (Gabriel et al., 1991; Garcia Rodriguez & Hernandez-Diaz, 2001). For example, in a 5-year population-based cohort study of 958,397 persons in the United Kingdom, the relative risk of upper gastrointestinal bleeding and/or perforation was 2.4 (95% CI, 1.9-3.1) among patients who used low or medium doses of NSAIDs and 4.9 (95% CI, 4.1-5.8) among patients who used high doses of NSAIDs compared with non-users of NSAIDs. The use of gastroprotectants, such as proton pump inhibitors and misoprostol, reduces these risks (Garcia Rodriguez & Hernandez-Diaz, 2001), and many osteoarthritis treatment guidelines recommend the co-prescription of gastroprotectants when nonselective NSAIDs are used to manage pain, especially in patients who are at an increased risk of gastrointestinal complications (ie, elderly patients, patients with a history of gastrointestinal bleeding or ulcer disease, patients on a low-dose aspirin regimen, and patients with a history of alcohol consumption; Jordan et al., 2003; Pham & Hirschberg, 2005; Zhang et al., 2008). Because elderly patients have an increased risk of gastrointestinal complications associated with NSAIDs, the 2009 American Geriatrics Society Clinical Practice Guideline for the Pharmacological Management of Persistent Pain in Older Adults recommends that nonselective NSAIDs and COX-2 selective inhibitors be considered rarely, with caution, and only in highly selected individuals (American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons, 2009).

Selective COX-2 inhibitors are associated with a substantially reduced risk of gastrointestinal complications relative to nonselective NSAIDs (Pham & Hirschberg, 2005). However, selective COX-2 inhibitors are associated with an increased risk of cardiovascular events (eg, myocardial infarction and stroke), and 2 widely used COX-2 inhibitors, rofecoxib and valdecoxib, were withdrawn from the market due to concerns about their cardiovascular safety (Altman, 2009; Andersohn et al., 2006; Caldwell et al., 2006). The cardiovascular risks associated with selective COX-2 inhibitors have been confirmed by the results of several studies (Bombardier et al., 2000; Bresalier et al., 2005; Graham et al., 2005; Nussmeier et al., 2005; Solomon et al., 2005), and in recent years these findings have been extended to nonselective NSAIDs, particularly diclofenac (Fosbol et al., 2009; Gislason et al., 2009; Hammad et al., 2008; McGettigan & Henry, 2006; Schjerning Olsen et al., 2011). In patients with a history of myocardial infarction, Schjerning Olsen and colleagues observed that NSAID treatment durations ranging from less than 7 days to more than 90 days were associated with significantly increased risks of death and recurrent myocardial infarction. All of the NSAIDs analyzed in this study (ie, rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, and other NSAIDs) were associated with a significantly increased risk of death. Diclofenac was associated with the earliest onset and highest relative risk of



death/recurrent myocardial infarction, while the lowest risks were observed with naproxen (Schjerning Olsen et al., 2011).

NSAIDs are also available as topical preparations (Altman, 2010; Barthel & Oxford-Gatley, 2010). Topical formulations are believed to provide analgesia via the same mechanisms as oral NSAIDs, with similar efficacy but with reduced systemic exposure and, hence, fewer treatment-related side effects (Barthel & Oxford-Gatley, 2010). Osteoarthritis treatment guidelines issued by the UK National Institute for Health and Clinical Excellence recommend that topical NSAIDs, possibly in combination with acetaminophen, should be considered as second-line therapy after acetaminophen alone and before oral nonselective NSAIDs, selective COX-2 inhibitors, or opioids (The National Collaborating Centre for Chronic Conditions, 2008). In the United States, the only 2 topical NSAID formulations approved for the management of osteoarthritis pain are diclofenac sodium 1% gel and diclofenac sodium 1.5% in 45.5% dimethylsulfoxide (Altman & Smith, 2010; Barthel & Oxford-Gatley, 2010).

#### **2.2.4 Intra-articular injections**

Intra-articular injections of hyaluronic acid have demonstrated efficacy for the management of knee osteoarthritis pain; however, data on the use of intra-articular hyaluronic acid in hip and other types of osteoarthritis are limited (Goldberg & Buckwalter, 2005; Jordan et al., 2003; Neustadt, 2006). Hyaluronic acid is a high molecular weight glucosaminoglycan present in high concentrations in synovial fluid. It has lubricating and viscoelastic properties, which reduce articular cartilage friction. In osteoarthritis, the synthesis of hyaluronic acid is altered; ie, total concentration is decreased and molecular chain length is reduced. In patients with knee osteoarthritis, intra-articular injections of hyaluronic acid have been shown to reduce synovial fluid viscosity and to reduce pain by several different mechanisms. Hyaluronic acid may slow the progression of disease by improving synovite and chondrocyte function and by modifying the structure of damaged matrix proteins, collagen, and articular cartilage (Goldberg & Buckwalter, 2005). Injectable hyaluronic acid formulations are not associated with any major safety concerns; however, minor AEs, including transient injection-site pain, have been observed in clinical trials (Arrich et al., 2005; Bellamy et al., 2006b).

Intra-articular injections of corticosteroids have been used for more than 50 years for the treatment of osteoarthritis and other rheumatic diseases (Bannuru et al., 2011; Neustadt, 2006). Osteoarthritis treatment guidelines recommend that intra-articular corticosteroids should be considered in patients with moderate to severe pain who have not responded to oral analgesics (Jordan et al., 2003). Intra-articular corticosteroids often provide substantial and lasting osteoarthritis pain relief, and may reduce the inflammatory cell-mediated degradation of articular cartilage (Neustadt, 2006). The short-term benefits of intra-articular corticosteroids are well established; however, the long-term benefits remain unclear (Bellamy et al., 2006a). Intra-articular corticosteroids are generally well tolerated; the most common side effects associated with intra-articular corticosteroid use are post-injection flares of pain, crystal synovitis, haemarthrosis (Bellamy et al., 2006a), joint sepsis, and articular atrophy. These side effects are usually not serious (Bellamy et al., 2006a; Jordan et al., 2003). It is important that intra-articular corticosteroid injections are placed correctly to avoid the possible AEs of fat necrosis and para-articular tissue atrophy (Jones et al., 1993), and injections should not be repeated more than 4 times per year (Jordan et al., 2003).

In a meta-analysis comparing the analgesic efficacy of intra-articular hyaluronic acid versus intra-articular corticosteroids in patients with knee osteoarthritis, Bannuru and colleagues found that during the first 4 weeks of treatment, corticosteroids were more effective than hyaluronic acid (effect size at Week 2,  $-0.39$  [95% CI,  $-0.65$  to  $-0.12$ ]), but by Week 4, the 2 treatments were not statistically different (effect size,  $-0.01$  [95% CI,  $-0.23$  to  $0.21$ ]). After more than 8 weeks of treatment, the efficacy of hyaluronic acid was superior to that of corticosteroids (effect size at Week 12,  $0.35$  [95% CI,  $0.03$ - $0.66$ ]; at Week 26,  $0.39$  [95% CI,  $0.18$ - $0.59$ ]; Bannuru et al., 2011).

### 2.2.5 SNRIs

Because osteoarthritis pain perception can have a central sensitization component (Arendt-Nielsen et al., 2010; Gwilym et al., 2009; Hochman et al., 2010; Woolf, 2011), recent studies have investigated the analgesic efficacy of the SNRI duloxetine for the management of chronic osteoarthritis pain (Chappell et al., 2009; Chappell et al., 2011; Sullivan et al., 2009). In 2 randomized, double-blind, placebo-controlled trials in patients with moderate to severe osteoarthritis knee pain ( $n = 231$  and  $n = 256$ , respectively), 13 weeks of treatment with duloxetine (60-120 mg/day) was associated with significantly reduced weekly average 24-hour pain scores and significant improvements in Western Ontario and McMaster Universities (WOMAC) osteoarthritis index physical functioning scores (Chappell et al., 2009; Chappell et al., 2011). Duloxetine was associated with significantly higher incidences of nausea, constipation, and hyperhidrosis (all  $P \leq 0.05$ ) and a significantly higher rate of discontinuation due to AEs ( $P = 0.002$ ) compared with placebo (Chappell et al., 2011).

In August 2010, the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) of the US Food & Drug Administration (FDA) recommended approval of duloxetine hydrochloride (60 mg/day) for the management of chronic musculoskeletal pain by a vote of 8 to 6 (US Food and Drug Administration, 2010), and duloxetine is currently being marketed as a treatment for chronic osteoarthritis pain (CYMBALTA, 2011). However, at the same FDA meeting, the ALSDAC voted 9 to 4 (with 1 abstention) against the use of duloxetine for the management of chronic osteoarthritis pain. The committee expressed views that data from clinical trials in patients with chronic osteoarthritis pain did not provide adequate evidence supporting the analgesic efficacy of duloxetine in this population. The committee recommended that additional studies involving more patients should be conducted to confirm the efficacy of duloxetine for the management of chronic osteoarthritis pain (US Food and Drug Administration, 2010).

While the role of SNRIs in the management of osteoarthritis pain remains unclear, results from duloxetine trials published to date (Chappell et al., 2009; Chappell et al., 2011; Sullivan et al., 2009) suggest that central sensitization may play a significant role in pain perception in patients with chronic osteoarthritis pain.

### 2.2.6 Opioids

Weak opioid analgesics (eg, codeine, dihydrocodeine, tramadol) are recommended for the management of osteoarthritis pain in patients who have failed to respond to other pharmacologic or nonpharmacologic treatments, or when other analgesics are contraindicated (Zhang et al., 2008; Zhang et al., 2010). Strong opioids (eg, oxycodone, morphine, fentanyl, hydromorphone, oxymorphone, buprenorphine) are recommended for the management of severe osteoarthritis pain only when appropriate nonpharmacologic and

pharmacologic treatments have been tried and referral for surgery has been considered (Zhang et al., 2008). Opioids can be used alone or in combination with acetaminophen or aspirin (Dominick et al., 2004; Jordan et al., 2003).

In recent years, the number of prescriptions for opioid analgesics for the management of chronic non-cancer pain has increased dramatically (Altman & Smith, 2010). According to the Trends and Risks of Opioid Use for Pain study, between 2000 and 2005, among patients with commercial health insurance who were diagnosed with chronic back pain, neck pain, joint/arthritis pain, headache pain, or pain associated with HIV/AIDS, the number of opioid prescriptions increased by 58%. During this time period, the number of eligible patients diagnosed with one of these painful conditions increased by 33%, from 18% (485,794/2,716,163) in 2000 to 24% (897,537/3,768,223) in 2005. Thus, the increase in opioid prescriptions is only partially explained by an increasing incidence of chronic pain conditions (Sullivan et al., 2008). Further, in a 1-year study of opioid prescriptions among patients in the Veterans Affairs healthcare system, of 3,061 patients who visited a physician for osteoarthritis, 41% had at least 1 opioid prescription (Dominick et al., 2004). These results suggest that opioids are increasingly gaining acceptance as a treatment option for chronic osteoarthritis pain (Altman & Smith, 2010; Dominick et al., 2004; Sullivan et al., 2008).

In clinical trials, opioids have demonstrated efficacy for the management of moderate to severe osteoarthritis pain (Altman & Smith, 2010; Avouac et al., 2007; Caldwell et al., 2002; Matsumoto et al., 2005; Nuesch et al., 2009; Roth et al., 2000). In a meta-analysis of 13 randomized placebo-controlled trials of orally or transdermally administered opioids (oxycodone, fentanyl, morphine sulfate, tramadol, tramadol/acetaminophen, or codeine) that included a total of 3,733 patients with osteoarthritis pain, the pooled effect size of opioids compared with placebo for pain intensity reduction was  $-0.79$  (95% CI,  $-0.98$  to  $-0.59$ ) based on a random-effects model (Avouac et al., 2007).

Opioid treatment has also been associated with significant improvements in physical function and quality of life (Avouac et al., 2007; Caldwell et al., 2002; Hale et al., 2007; Matsumoto et al., 2005; Nuesch et al., 2009; Rosenthal et al., 2007; Roth et al., 2000). Improvements in WOMAC scores have been observed in studies of fentanyl, oxycodone, oxycodone/acetaminophen, morphine sulfate, oxymorphone, and hydromorphone for osteoarthritis pain (Caldwell et al., 2002; Hale et al., 2007; Katz et al., 2010; Langford et al., 2006; Matsumoto et al., 2005). In addition, improvements in sleep, mood, and enjoyment of life have been associated with opioid analgesic therapy for the management of chronic osteoarthritis pain (Rosenthal et al., 2007; Roth et al., 2000).

In spite of the improvements observed in pain intensity, physical function, and health-related quality of life associated with opioid analgesics, the long-term use of these agents may be limited by poor tolerability (Benyamin et al., 2008). In an open-label extension study lasting 6 to 18 months (following an initial 14-day placebo-controlled study) of oxycodone controlled release (CR; 10 or 20 mg bid) for the treatment of moderate to severe, chronic osteoarthritis pain, 57% (60/106) of patients discontinued treatment, and more than half of these discontinuations (32/60) were related to AEs (Roth et al., 2000). The most common AEs leading to discontinuation were constipation, nausea, pruritus, somnolence, and nervousness. These AEs were also among the most commonly reported treatment-emergent AEs (TEAEs). During this 6- to 18-month long-term extension trial, 52% (55/106) of patients taking oxycodone CR reported constipation, 30% (32/106) reported somnolence, 24% (25/106) reported nausea, 20% (21/106) reported pruritus, and 15% (16/106) reported nervousness (Roth et al., 2000).

In a Cochrane review of 10 trials (n = 2,268) that studied codeine, morphine, oxycodone, oxymorphone, or fentanyl for the management of osteoarthritis hip or knee pain, Nüesch and colleagues found that while opioids were more effective than controls (standardized mean difference, -0.36; 95% CI, -0.47 to -0.26), opioids were associated with a significantly increased risk of AEs (pooled risk ratio, 1.55; 95% CI, 1.41-1.70) and of dropout due to AEs (pooled risk ratio, 4.05; 95% CI, 3.06-5.38) compared with controls. The authors concluded that the small to moderate beneficial effects associated with opioids for the management of chronic osteoarthritis pain do not outweigh the significantly increased risk of AEs (Nüesch et al., 2009).

### **2.2.7 New treatment option: Tapentadol extended release, a $\mu$ -opioid receptor agonist and norepinephrine reuptake inhibitor**

Tapentadol is a new, centrally acting analgesic that has  $\mu$ -opioid receptor agonist and norepinephrine reuptake inhibitor activities (Tzschentke et al., 2006; Tzschentke et al., 2007). The opioid activity of tapentadol targets nociceptive pain at the joint level, while norepinephrine reuptake inhibition targets referred pain caused by central sensitization. In the United States, an extended-release formulation of tapentadol is in development for the management of moderate to severe chronic pain. In Europe, a prolonged-release formulation is indicated for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics.

In preclinical studies, tapentadol has demonstrated efficacy in models of both neuropathic and nociceptive pain (Tzschentke et al., 2007). In addition, it has been observed that tapentadol's 2 mechanisms of action act synergistically to produce potent analgesia that is greater than the predicted additive effects of the 2 mechanisms. These synergistic effects are particularly notable in models of chronic pain, possibly because chronic pain is more likely than acute pain to have both noradrenergic and nociceptive components (Schroder et al., 2011). The 2 mechanisms of action of tapentadol affect both the ascending and descending pathways of central nervous system pain control, which may make it an appropriate treatment option for patients with chronic osteoarthritis who experience both nociceptive pain and pain caused by central sensitization.

The efficacy of tapentadol extended release (ER) has been demonstrated in patients with moderate to severe, chronic osteoarthritis pain (Afilalo et al., 2010). In a 15-week randomized, placebo- and active-controlled, phase 3 study in patients with moderate to severe, chronic osteoarthritis knee pain (n = 1,023), tapentadol ER (100-250 mg bid) provided significantly better pain relief compared with placebo (least-squares mean difference in average pain intensity from baseline to Week 12 measured on an 11-point numerical rating scale, -0.7; 95% CI, -1.04 to -0.33; Afilalo et al., 2010). Tapentadol ER was associated with significant improvements in overall health, pain, and physical function compared with placebo based on the Short Form-36 (SF-36) and EuroQol-5 Dimension (EQ-5D) health status scores. Patients treated with tapentadol ER also scored significantly better on the global WOMAC and on pain and physical function WOMAC subscales compared with placebo, indicating that tapentadol ER treatment was associated with robust improvement in analgesia and overall physical function (Afilalo et al., 2010). In this study, the efficacy of tapentadol ER was particularly notable when it was administered to patients who had not received opioid analgesics within the 3 months prior to the study. Opioid-naïve patients treated with tapentadol ER achieved statistically significant improvements from baseline in

average pain intensity, while patients treated with oxycodone CR did not. In opioid-naïve patients in the tapentadol ER and oxycodone CR groups, respectively, gastrointestinal TEAEs were reported by 47.7% and 67.5% of patients, and 19.6% and 48.3% of patients discontinued due to AEs (Etropolski et al., 2009).

In a 1-year, randomized, open-label, phase 3 long-term safety study in patients with moderate to severe, chronic osteoarthritis hip or knee pain or low back pain, tapentadol ER (100-250 mg bid) was shown to have comparable analgesic efficacy to oxycodone HCl CR (20-50 mg bid), but tapentadol ER was associated with better overall tolerability and lower incidences of side effects and TEAE-related discontinuations (Figure 1). Tapentadol ER was associated with particularly better gastrointestinal tolerability compared with oxycodone CR. Gastrointestinal TEAEs led to discontinuation in 8.6% (77/894) of patients in the tapentadol ER group compared with 21.5% (48/223) of patients in the oxycodone CR group (Wild et al., 2010).

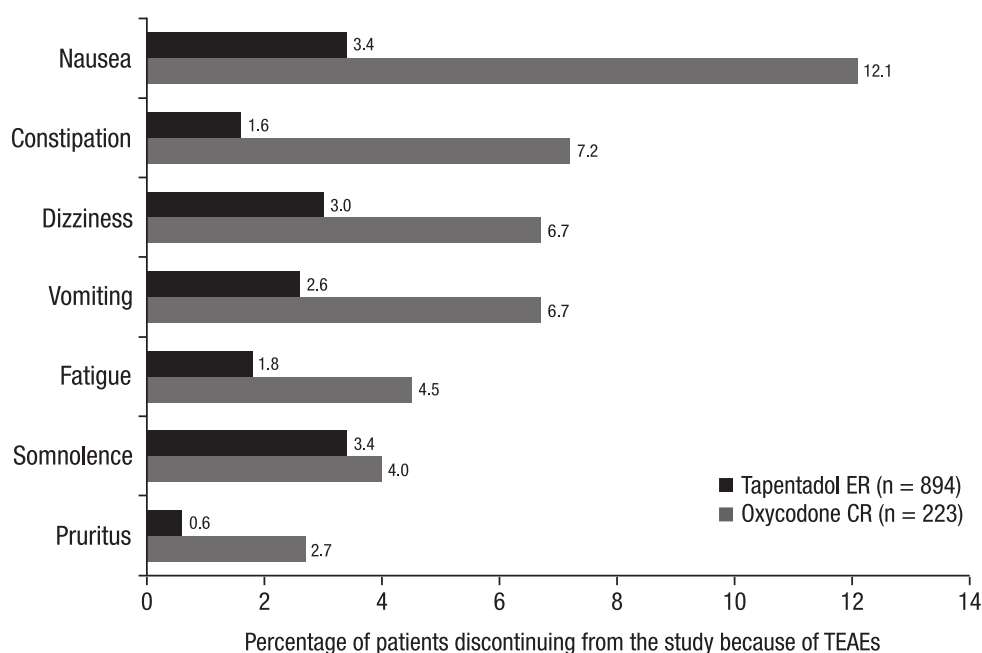


Fig. 1. TEAE-related discontinuations in a 1-year safety study of tapentadol ER (100-250 mg bid) compared with oxycodone HCl CR (20-50 mg bid). Reprinted from *Pain Practice*, Vol 10, Wild JE, et al, Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain, pp. 416-427 (2010), with permission from John Wiley and Sons. TEAE, treatment-emergent adverse event; ER, extended release; CR, controlled release.

In pooled analyses of data from 3 randomized, placebo- and active-controlled, phase 3 studies with 15 weeks of active treatment in patients with moderate to severe, chronic osteoarthritis knee pain (2 studies) or low back pain (1 study), the efficacy of tapentadol ER (100-250 mg bid) was non-inferior to that of oxycodone HCl CR (20-50 mg bid); however, tapentadol ER had a superior gastrointestinal tolerability profile relative to oxycodone CR (Lange et al., 2010). Tapentadol ER treatment was associated with fewer discontinuations from treatment compared with oxycodone CR and significant improvements in function and quality of life based on SF-36 and EQ-5D health status questionnaire results. Improvements observed in 7 of 8 SF-36 domains and the EQ-5D health status index score were significantly

better with tapentadol ER (100-250 mg bid) compared with oxycodone HCl CR (20-50 mg bid; Lange et al., 2010).

The health status and WOMAC functional improvements observed in these studies are likely associated with the improved tolerability profile of tapentadol ER compared with oxycodone CR. The superior tolerability of tapentadol ER may have allowed patients to maintain their therapy and to sustain the achieved analgesic effect for a longer period of time compared with oxycodone CR. Oxycodone CR was associated with a higher rate of discontinuations and worse tolerability compared with tapentadol ER (Afilalo et al., 2010; Lange et al., 2010).

### 3. Conclusion

Nonpharmacologic approaches, including exercise and weight-loss programs, have been shown to reduce pain and psychological disability in patients with osteoarthritis, and should be an integral part of all osteoarthritis treatment plans (Felson et al., 2000; Klusmann et al., 2010; Messier, 2008; Physical Activity Guidelines Advisory Committee, 2008). Guidelines for the pharmacologic management of osteoarthritis pain recommend a stepwise approach to therapy, initiating with acetaminophen, then transitioning to NSAIDs and finally to opioids if prior therapy fails (Jordan et al., 2003; Zhang et al., 2008). However, the long-term utility of NSAIDs and opioid analgesics may be limited by safety and tolerability issues (Benyamin et al., 2008; Zhang et al., 2008).

Tapentadol ER provides effective pain control with good tolerability and improvements in quality of life (Afilalo et al., 2010; Lange et al., 2010; Wild et al., 2010). The favorable tolerability profile of tapentadol ER compared with oxycodone CR may allow patients to remain on treatment for longer periods of time, resulting in consistent, effective pain relief and long-term improvements in quality of life and health status. Because tapentadol acts as both a  $\mu$ -opioid receptor agonist and as a norepinephrine reuptake inhibitor, tapentadol ER may relieve both nociceptive pain and neuropathic pain associated with central sensitization. Thus, tapentadol ER may be an effective treatment option that has better tolerability than pure  $\mu$ -opioid analgesics in patients with moderate to severe, chronic osteoarthritis pain.

### 4. Acknowledgment

Editorial support for the writing of this chapter was provided by Megan Knagge, PhD, of MedErgy and was funded by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. The author retained full editorial control over the content.

### 5. References

- Abramson, S.B. & Attur, M. (2009). Developments in the Scientific Understanding of Osteoarthritis. *Arthritis Research & Therapy*, Vol.11, No.3, p. 227, ISSN 1478-6354
- Afilalo, M., Etropolski, M.S., Kuperwasser, B., Kelly, K., Okamoto, A., Van, H., I, Steup, A., Lange, B., Rauschkolb, C. & Haeussler, J. (2010). Efficacy and Safety of Tapentadol Extended Release Compared With Oxycodone Controlled Release for the Management of Moderate to Severe Chronic Pain Related to Osteoarthritis of the

- Knee: a Randomized, Double-Blind, Placebo- and Active-Controlled Phase III Study. *Clinical Drug Investigation*, Vol.30, No.8, pp. 489-505, ISSN 1173-2563
- Altman, R.D. (2010). New Guidelines for Topical NSAIDs in the Osteoarthritis Treatment Paradigm. *Current Medical Research & Opinion*, Vol.26, No.12, pp. 2871-2876, ISSN 0300-7995
- Altman, R.D. (2009). Practical Considerations for the Pharmacologic Management of Osteoarthritis. *American Journal of Managed Care*, Vol.15, No.8 Suppl, p. S236-S243, ISSN 1936-2692
- Altman, R.D. & Smith, H.S. (2010). Opioid Therapy for Osteoarthritis and Chronic Low Back Pain. *Postgraduate Medicine*, Vol.122, No.6, pp. 87-97, ISSN 0032-5481
- American College of Rheumatology. (2000). Recommendations for the Medical Management of Osteoarthritis of the Hip and Knee: 2000 Update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. *Arthritis and Rheumatism*, Vol.43, No.9, pp. 1905-1915, ISSN 1529-0131
- American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. (2009). Pharmacological Management of Persistent Pain in Older Persons. *Journal of the American Geriatrics Society*, Vol.57, No.8, pp. 1331-1346, ISSN 0002-8614
- Andersohn, F., Suissa, S. & Garbe, E. (2006). Use of First- and Second-Generation Cyclooxygenase-2-Selective Nonsteroidal Antiinflammatory Drugs and Risk of Acute Myocardial Infarction. *Circulation*, Vol.113, No.16, pp. 1950-1957, ISSN 0009-7322
- Arendt-Nielsen, L., Nie, H., Laursen, M.B., Laursen, B.S., Madeleine, P., Simonsen, O.H. & Graven-Nielsen, T. (2010). Sensitization in Patients With Painful Knee Osteoarthritis. *Pain*, Vol.149, No.3, pp. 573-581, ISSN 0304-3959
- Arrich, J., Piribauer, F., Mad, P., Schmid, D., Klaushofer, K. & Mullner, M. (2005). Intra-Articular Hyaluronic Acid for the Treatment of Osteoarthritis of the Knee: Systematic Review and Meta-Analysis. *Canadian Medical Association Journal*, Vol.172, No.8, pp. 1039-1043, ISSN 0820-3946
- Avouac, J., Gossec, L. & Dougados, M. (2007). Efficacy and Safety of Opioids for Osteoarthritis: a Meta-Analysis of Randomized Controlled Trials. *Osteoarthritis and Cartilage*, Vol.15, No.8, pp. 957-965, ISSN 1063-4584
- Axford, J., Heron, C., Ross, F. & Victor, C.R. (2008). Management of Knee Osteoarthritis in Primary Care: Pain and Depression Are the Major Obstacles. *J Psychosom Res*, Vol.64, No.5, pp. 461-467, ISSN 0022-3999
- Bannuru, R.R., Natov, N.S., Dasi, U.R., Schmid, C.H. & McAlindon, T.E. (2011). Therapeutic Trajectory Following Intra-Articular Hyaluronic Acid Injection in Knee Osteoarthritis - Meta-Analysis. *Osteoarthritis and Cartilage*, ISSN 1063-4584
- Barron, M.C. & Rubin, B.R. (2007). Managing Osteoarthritic Knee Pain. *Journal of the American Osteopathic Association*, Vol.107, No.10 Suppl 6, p. ES21-ES27, ISSN 0098-6151
- Barthel, H.R. & Oxford-Gatley, R.A. (2010). Topical Nonsteroidal Anti-Inflammatory Drugs for Osteoarthritis. *Postgraduate Medicine*, Vol.122, No.6, pp. 98-106, ISSN 0032-5481
- Bellamy, N., Campbell, J., Robinson, V., Gee, T., Bourne, R. & Wells, G. (2006a). Intraarticular Corticosteroid for Treatment of Osteoarthritis of the Knee. *Cochrane Database of Systemic Reviews*, No.2, p. CD005328

- Bellamy, N., Campbell, J., Robinson, V., Gee, T., Bourne, R. & Wells, G. (2006b). Viscosupplementation for the Treatment of Osteoarthritis of the Knee. *Cochrane Database of Systemic Reviews*, No.2, p. CD005321
- Benyamin, R., Trescot, A.M., Datta, S., Buenaventura, R., Adlaka, R., Sehgal, N., Glaser, S.E. & Vallejo, R. (2008). Opioid Complications and Side Effects. *Pain Physician*, Vol.11, No.2 suppl, p. S105-S120, ISSN 1533-3159
- Bjordal, J.M., Ljunggren, A.E., Klovning, A. & Slordal, L. (2004). Non-Steroidal Anti-Inflammatory Drugs, Including Cyclo-Oxygenase-2 Inhibitors, in Osteoarthritic Knee Pain: Meta-Analysis of Randomised Placebo Controlled Trials. *British Medical Journal*, Vol.329, No.7478, p. 1317, ISSN 0959-8138
- Bombardier, C., Laine, L., Reicin, A., Shapiro, D., Burgos-Vargas, R., Davis, B., Day, R., Ferraz, M.B., Hawkey, C.J., Hochberg, M.C., Kvien, T.K., Schnitzer, T.J. & for the VIGOR Study Group. (2000). Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients With Rheumatoid Arthritis. *New England Journal of Medicine*, Vol.343, No.21, pp. 1520-1528, ISSN 0028-4793
- Boureau, F., Schneid, H., Zeghari, N., Wall, R. & Bourgeois, P. (2004). The IPSO Study: Ibuprofen, Paracetamol Study in Osteoarthritis. A Randomised Comparative Clinical Study Comparing the Efficacy and Safety of Ibuprofen and Paracetamol Analgesic Treatment of Osteoarthritis of the Knee or Hip. *Annals of the Rheumatic Diseases*, Vol.63, No.9, pp. 1028-1034, ISSN 0003-4967
- Breedveld, F.C. (2004). Osteoarthritis--the Impact of a Serious Disease. *Rheumatology (Oxford)*, Vol.43, No.suppl 1, p. i4-i8, ISSN 1462-0324
- Bresalier, R.S., Sandler, R.S., Quan, H., Bolognese, J.A., Oxenius, B., Horgan, K., Lines, C., Riddell, R., Morton, D., Lanus, A., Konstam, M.A. & Baron, J.A. (2005). Cardiovascular Events Associated With Rofecoxib in a Colorectal Adenoma Chemoprevention Trial. *New England Journal of Medicine*, Vol.352, No.11, pp. 1092-1102, ISSN 0028-4793
- Caldwell, B., Aldington, S., Weatherall, M., Shirtcliffe, P. & Beasley, R. (2006). Risk of Cardiovascular Events and Celecoxib: a Systematic Review and Meta-Analysis. *Journal of the Royal Society of Medicine*, Vol.99, No.3, pp. 132-140, ISSN 0141-0768
- Caldwell, J.R., Rapoport, R.J., Davis, J.C., Offenberg, H.L., Marker, H.W., Roth, S.H., Yuan, W., Eliot, L., Babul, N. & Lynch, P.M. (2002). Efficacy and Safety of a Once-Daily Morphine Formulation in Chronic, Moderate-to-Severe Osteoarthritis Pain: Results From a Randomized, Placebo-Controlled, Double-Blind Trial and an Open-Label Extension Trial. *Journal of Pain and Symptom Management*, Vol.23, No.4, pp. 278-291, ISSN 0885-3924
- Catala, E., Reig, E., Artes, M., Aliaga, L., Lopez, J.S. & Segú, J.L. (2002). Prevalence of Pain in the Spanish Population: Telephone Survey in 5000 Homes. *European Journal of Pain*, Vol.6, No.2, pp. 133-140, ISSN 1090-3801
- Chappell, A.S., Desai, D., Liu-Seifert, H., Zhang, S., Skljarevski, V., Belenkov, Y. & Brown, J.P. (2011). 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 Practice*, Vol.11, No.1, pp. 33-41, ISSN 1530-7085
- Chappell, A.S., Ossanna, M.J., Liu-Seifert, H., Iyengar, S., Skljarevski, V., Li, L.C., Bennett, R.M. & Collins, H. (2009). Duloxetine, a Centrally Acting Analgesic, in the



- Treatment of Patients With Osteoarthritis Knee Pain: a 13-Week, Randomized, Placebo-Controlled Trial. *Pain*, Vol.146, No.3, pp. 253-260, ISSN 0304-3959
- Christensen, R., Bartels, E.M., Astrup, A. & Bliddal, H. (2007). Effect of Weight Reduction in Obese Patients Diagnosed With Knee Osteoarthritis: a Systematic Review and Meta-Analysis. *Annals of the Rheumatic Diseases*, Vol.66, No.4, pp. 433-439, ISSN 0003-4967
- Coleman, S., McQuade, J., Rose, J., Inderjeeth, C., Carroll, G. & Briffa, N.K. (2010). Self-Management for Osteoarthritis of the Knee: Does Mode of Delivery Influence Outcome? *BMC Musculoskeletal Disorders*, Vol.11, p. 56
- Courtney, C.A., Kavchak, A.E., Lowry, C.D. & O'Hearn, M.A. (2010). Interpreting Joint Pain: Quantitative Sensory Testing in Musculoskeletal Management. *Journal of Orthopaedic and Sports Physical Therapy*, Vol.40, No.12, pp. 818-825, ISSN 0190-6011
- Crofford, L.J. (1997). COX-1 and COX-2 Tissue Expression: Implications and Predictions. *Journal of Rheumatology Supplement*, Vol.49, pp. 15-19, ISSN 0380-0903
- CYMBALTA® (Duloxetine Hydrochloride) Delayed-Release Capsules [Package Insert]. Indianapolis, In: Eli Lilly and Company; 2011
- de Bock, G.H., Kaptein, A.A., Touw-Otten, F. & Mulder, J.D. (1995). Health-Related Quality of Life in Patients With Osteoarthritis in a Family Practice Setting. *Arthritis Care and Research*, Vol.8, No.2, pp. 88-93, ISSN 0893-7524
- Dillon, C.F., Rasch, E.K., Gu, Q. & Hirsch, R. (2006). Prevalence of Knee Osteoarthritis in the United States: Arthritis Data From the Third National Health and Nutrition Examination Survey 1991-94. *Journal of Rheumatology*, Vol.33, No.11, pp. 2271-2279, ISSN 0315-162X
- Dominick, K.L., Bosworth, H.B., Dudley, T.K., Waters, S.J., Campbell, L.C. & Keefe, F.J. (2004). Patterns of Opioid Analgesic Prescription Among Patients With Osteoarthritis. *Journal of Pain & Palliative Care Pharmacotherapy*, Vol.18, No.1, pp. 31-46, ISSN 1536-0288
- Elliott, A.M., Smith, B.H., Penny, K.I., Smith, W.C. & Chambers, W.A. (1999). The Epidemiology of Chronic Pain in the Community. *Lancet*, Vol.354, No.9186, pp. 1248-1252, ISSN 0140-6736
- Etropolski, M., Lange, B., Kuperwasser, B., Kelly, K., Okamoto, A., Steup, A., Van Hove, I., Weber, H. & Häussler, J. (2009). Efficacy and Safety of Tapentadol Extended Release Versus Oxycodone Controlled Release in Opioid-Naive and Opioid-Experienced Patients With Chronic Pain Associated With Osteoarthritis of the Knee. *Osteoarthritis and Cartilage*, Vol.17, No.suppl 1, p. S175
- Felson, D.T. (2006). Clinical Practice. Osteoarthritis of the Knee. *New England Journal of Medicine*, Vol.354, No.8, pp. 841-848, ISSN 0028-4793
- Felson, D.T. (2009). Developments in the Clinical Understanding of Osteoarthritis. *Arthritis Research & Therapy*, Vol.11, No.1, p. 203, ISSN 1478-6354
- Felson, D.T., Lawrence, R.C., Dieppe, P.A., Hirsch, R., Helmick, C.G., Jordan, J.M., Kington, R.S., Lane, N.E., Nevitt, M.C., Zhang, Y., Sowers, M., McAlindon, T., Spector, T.D., Poole, A.R., Yanovski, S.Z., Ateshian, G., Sharma, L., Buckwalter, J.A., Brandt, K.D. & Fries, J.F. (2000). Osteoarthritis: New Insights. Part 1: the Disease and Its Risk Factors. *Annals of Internal Medicine*, Vol.133, No.8, pp. 635-646, ISSN 0003-4819

- Felson, D.T., Naimark, A., Anderson, J., Kazis, L., Castelli, W. & Meenan, R.F. (1987). The Prevalence of Knee Osteoarthritis in the Elderly. The Framingham Osteoarthritis Study. *Arthritis and Rheumatism*, Vol.30, No.8, pp. 914-918, ISSN 0004-3591
- Fendrick, A.M. & Greenberg, B.P. (2009). A Review of the Benefits and Risks of Nonsteroidal Anti-Inflammatory Drugs in the Management of Mild-to-Moderate Osteoarthritis. *Osteopathic Medicine and Primary Care*, Vol.3, p. 1
- Flood, J. (2010). The Role of Acetaminophen in the Treatment of Osteoarthritis. *American Journal of Managed Care*, Vol.16 Suppl Management, p. S48-S54, ISSN 1088-0224
- Fored, C.M., Ejerblad, E., Lindblad, P., Fryzek, J.P., Dickman, P.W., Signorello, L.B., Lipworth, L., Elinder, C.G., Blot, W.J., McLaughlin, J.K., Zack, M.M. & Nyren, O. (2001). Acetaminophen, Aspirin, and Chronic Renal Failure. *New England Journal of Medicine*, Vol.345, No.25, pp. 1801-1808, ISSN 0028-4793
- Fosbol, E.L., Gislason, G.H., Jacobsen, S., Folke, F., Hansen, M.L., Schramm, T.K., Sorensen, R., Rasmussen, J.N., Andersen, S.S., Abildstrom, S.Z., Traerup, J., Poulsen, H.E., Rasmussen, S., Kober, L. & Torp-Pedersen, C. (2009). Risk of Myocardial Infarction and Death Associated With the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Among Healthy Individuals: a Nationwide Cohort Study. *Clinical Pharmacology and Therapeutics*, Vol.85, No.2, pp. 190-197, ISSN 0009-9236
- Gabriel, S.E., Jaakkimainen, L. & Bombardier, C. (1991). Risk for Serious Gastrointestinal Complications Related to Use of Nonsteroidal Anti-Inflammatory Drugs. A Meta-Analysis. *Annals of Internal Medicine*, Vol.115, No.10, pp. 787-796, ISSN 0003-4819
- Garcia Rodriguez, L.A. & Hernandez-Diaz, S. (2001). Relative Risk of Upper Gastrointestinal Complications Among Users of Acetaminophen and Nonsteroidal Anti-Inflammatory Drugs. *Epidemiology*, Vol.12, No.5, pp. 570-576, ISSN 1044-3983
- Gislason, G.H., Rasmussen, J.N., Abildstrom, S.Z., Schramm, T.K., Hansen, M.L., Fosbol, E.L., Sorensen, R., Folke, F., Buch, P., Gadsboll, N., Rasmussen, S., Poulsen, H.E., Kober, L., Madsen, M. & Torp-Pedersen, C. (2009). Increased Mortality and Cardiovascular Morbidity Associated With Use of Nonsteroidal Anti-Inflammatory Drugs in Chronic Heart Failure. *Archives of Internal Medicine*, Vol.169, No.2, pp. 141-149, ISSN 0003-9926
- Goldberg, V.M. & Buckwalter, J.A. (2005). Hyaluronans in the Treatment of Osteoarthritis of the Knee: Evidence for Disease-Modifying Activity. *Osteoarthritis and Cartilage*, Vol.13, No.3, pp. 216-224, ISSN 1063-4584
- Golden, H.E., Moskowitz, R.W. & Minic, M. (2004). Analgesic Efficacy and Safety of Nonprescription Doses of Naproxen Sodium Compared With Acetaminophen in the Treatment of Osteoarthritis of the Knee. *American Journal of Therapeutics*, Vol.11, No.2, pp. 85-94, ISSN 1075-2765
- Graham, D.J., Campen, D., Hui, R., Spence, M., Cheetham, C., Levy, G., Shoor, S. & Ray, W.A. (2005). 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*, Vol.365, No.9458, pp. 475-481, ISSN 0140-6736
- Gregory, P.J., Sperry, M. & Wilson, A.F. (2008). Dietary Supplements for Osteoarthritis. *American Family Physician*, Vol.77, No.2, pp. 177-184, ISSN 0002-838X
- Gwilym, S.E., Keltner, J.R., Warnaby, C.E., Carr, A.J., Chizh, B., Chessell, I. & Tracey, I. (2009). Psychophysical and Functional Imaging Evidence Supporting the Presence

- of Central Sensitization in a Cohort of Osteoarthritis Patients. *Arthritis and Rheumatism*, Vol.61, No.9, pp. 1226-1234, ISSN 0004-3591
- Hale, M., Tudor, I.C., Khanna, S. & Thippawong, J. (2007). Efficacy and Tolerability of Once-Daily OROS Hydromorphone and Twice-Daily Extended-Release Oxycodone in Patients With Chronic, Moderate to Severe Osteoarthritis Pain: Results of a 6-Week, Randomized, Open-Label, Noninferiority Analysis. *Clinical Therapeutics*, Vol.29, No.5, pp. 874-888, ISSN 0149-2918
- Hammad, T.A., Graham, D.J., Staffa, J.A., Kornegay, C.J. & Dal Pan, G.J. (2008). Onset of Acute Myocardial Infarction After Use of Non-Steroidal Anti-Inflammatory Drugs. *Pharmacoepidemiology and Drug Safety*, Vol.17, No.4, pp. 315-321, ISSN 1053-8569
- Hardy, M.L., Coulter, I., Morton, S.C., Favreau, J., Venuturupalli, S., Chiappelli, F., Rossi, F., Orshansky, G., Jungvig, L.K., Roth, E.A., Suttorp, M.J. & Shekelle, P. (2003). S-Adenosyl-L-Methionine for Treatment of Depression, Osteoarthritis, and Liver Disease. *Evidence Report - Technology Assessment (Summary)*, No.64, pp. 1-3, ISSN 1530-440X
- Helmick, C.G., Felson, D.T., Lawrence, R.C., Gabriel, S., Hirsch, R., Kwoh, C.K., Liang, M.H., Kremers, H.M., Mayes, M.D., Merkel, P.A., Pillemer, S.R., Reveille, J.D. & Stone, J.H. (2008). Estimates of the Prevalence of Arthritis and Other Rheumatic Conditions in the United States. Part I. *Arthritis and Rheumatism*, Vol.58, No.1, pp. 15-25, ISSN 0004-3591
- Hinton, R., Moody, R.L., Davis, A.W. & Thomas, S.F. (2002). Osteoarthritis: Diagnosis and Therapeutic Considerations. *American Family Physician*, Vol.65, No.5, pp. 841-848, ISSN 0002-838X
- Hochman, J.R., French, M.R., Bermingham, S.L. & Hawker, G.A. (2010). The Nerve of Osteoarthritis Pain. *Arthritis Care & Research (Hoboken)*, Vol.62, No.7, pp. 1019-1023, ISSN 2151-464X
- Hunter, D.J. & Felson, D.T. (2006). Osteoarthritis. *British Medical Journal*, Vol.332, No.7542, pp. 639-642, ISSN 0959-8146
- Hunter, D.J., McDougall, J.J. & Keefe, F.J. (2008). The Symptoms of Osteoarthritis and the Genesis of Pain. *Rheumatic Diseases Clinics of North America*, Vol.34, No.3, pp. 623-643, ISSN 0889-857X
- Jinks, C., Jordan, K. & Croft, P. (2007). Osteoarthritis As a Public Health Problem: the Impact of Developing Knee Pain on Physical Function in Adults Living in the Community: (KNEST 3). *Rheumatology (Oxford)*, Vol.46, No.5, pp. 877-881, ISSN 1462-0324
- Johannes, C.B., Le, T.K., Zhou, X., Johnston, J.A. & Dworkin, R.H. (2010). The Prevalence of Chronic Pain in United States Adults: Results of an Internet-Based Survey. *Journal of Pain*, Vol.11, No.11, pp. 1230-1239, ISSN 1526-5900
- Jones, A., Regan, M., Ledingham, J., Pattrick, M., Manhire, A. & Doherty, M. (1993). Importance of Placement of Intra-Articular Steroid Injections. *British Medical Journal*, Vol.307, No.6915, pp. 1329-1330, ISSN 0959-8138
- Jordan, K.M., Arden, N.K., Doherty, M., Bannwarth, B., Bijlsma, J.W., Dieppe, P., Gunther, K., Hauselmann, H., Herrero-Beaumont, G., Kaklamanis, P., Lohmander, S., Leeb, B., Lequesne, M., Mazieres, B., Martin-Mola, E., Pavelka, K., Pendleton, A., Punzi, L., Serni, U., Swoboda, B., Verbruggen, G., Zimmerman-Gorska, I. & Dougados, M. (2003). EULAR Recommendations 2003: an Evidence Based Approach to the Management of Knee Osteoarthritis: Report of a Task Force of the Standing

- Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Annals of the Rheumatic Diseases*, Vol.62, No.12, pp. 1145-1155, ISSN 0003-4967
- Katz, N., Hale, M., Morris, D. & Stauffer, J. (2010). Morphine Sulfate and Naltrexone Hydrochloride Extended Release Capsules in Patients With Chronic Osteoarthritis Pain. *Postgraduate Medicine*, Vol.122, No.4, pp. 112-128, ISSN 0032-5481
- Kidd, B.L., Langford, R.M. & Wodehouse, T. (2007). Arthritis and Pain. Current Approaches in the Treatment of Arthritic Pain. *Arthritis Research & Therapy*, Vol.9, No.3, p. 214, ISSN 1478-6354
- Kim, J., Lee, E.Y., Koh, E.M., Cha, H.S., Yoo, B., Lee, C.K., Lee, Y.J., Ryu, H., Lee, K.H. & Song, Y.W. (2009). Comparative Clinical Trial of S-Adenosylmethionine Versus Nabumetone for the Treatment of Knee Osteoarthritis: an 8-Week, Multicenter, Randomized, Double-Blind, Double-Dummy, Phase IV Study in Korean Patients. *Clinical Therapeutics*, Vol.31, No.12, pp. 2860-2872, ISSN 0149-2918
- Klussmann, A., Gebhardt, H., Nubling, M., Liebers, F., Quiros, P.E., Cordier, W., von Engelhardt, L.V., Schubert, M., David, A., Bouillon, B. & Rieger, M.A. (2010). Individual and Occupational Risk Factors for Knee Osteoarthritis: Results of a Case-Control Study in Germany. *Arthritis Research & Therapy*, Vol.12, No.3, p. R88, ISSN 1478-6354
- Kopec, J.A., Rahman, M.M., Berthelot, J.M., Le, P.C., Aghajanian, J., Sayre, E.C., Cibere, J., Anis, A.H. & Badley, E.M. (2007). Descriptive Epidemiology of Osteoarthritis in British Columbia, Canada. *Journal of Rheumatology*, Vol.34, No.2, pp. 386-393, ISSN 0315-162X
- Kosek, E. & Ordeberg, G. (2000). Abnormalities of Somatosensory Perception in Patients With Painful Osteoarthritis Normalize Following Successful Treatment. *European Journal of Pain*, Vol.4, No.3, pp. 229-238, ISSN 1090-3801
- Kotlarz, H., Gunnarsson, C.L., Fang, H. & Rizzo, J.A. (2009). Insurer and Out-of-Pocket Costs of Osteoarthritis in the US: Evidence From National Survey Data. *Arthritis and Rheumatism*, Vol.60, No.12, pp. 3546-3553, ISSN 0004-3591
- Lange, B., Kuperwasser, B., Okamoto, A., Steup, A., Haufel, T., Ashworth, J. & Etropolski, M. (2010). Efficacy and Safety of Tapentadol Prolonged Release for Chronic Osteoarthritis Pain and Low Back Pain. *Advances in Therapy*, Vol.27, No.6, pp. 381-399, ISSN 0741-238X
- Langford, R., McKenna, F., Ratcliffe, S., Vojtassak, J. & Richarz, U. (2006). Transdermal Fentanyl for Improvement of Pain and Functioning in Osteoarthritis: a Randomized, Placebo-Controlled Trial. *Arthritis and Rheumatism*, Vol.54, No.6, pp. 1829-1837, ISSN 0004-3591
- Lawrence, R.C., Felson, D.T., Helmick, C.G., Arnold, L.M., Choi, H., Deyo, R.A., Gabriel, S., Hirsch, R., Hochberg, M.C., Hunder, G.G., Jordan, J.M., Katz, J.N., Kremers, H.M. & Wolfe, F. (2008). Estimates of the Prevalence of Arthritis and Other Rheumatic Conditions in the United States. Part II. *Arthritis and Rheumatism*, Vol.58, No.1, pp. 26-35, ISSN 0004-3591
- Lee, C., Straus, W.L., Balshaw, R., Barlas, S., Vogel, S. & Schnitzer, T.J. (2004). A Comparison of the Efficacy and Safety of Nonsteroidal Antiinflammatory Agents Versus Acetaminophen in the Treatment of Osteoarthritis: a Meta-Analysis. *Arthritis and Rheumatism*, Vol.51, No.5, pp. 746-754, ISSN 0004-3591

- Loeser, R.F. (2008). Molecular Mechanisms of Cartilage Destruction in Osteoarthritis. *Journal of Musculoskeletal and Neuronal Interactions*, Vol.8, No.4, pp. 303-306, ISSN 1108-7161
- Majani, G., Giardini, A. & Scotti, A. (2005). Subjective Impact of Osteoarthritis Flare-Ups on Patients' Quality of Life. *Health and Quality of Life Outcomes*, Vol.3, p. 14
- Martel-Pelletier, J. & Pelletier, J.P. (2010). Is Osteoarthritis a Disease Involving Only Cartilage or Other Articular Tissues? *Eklem Hastalik Cerrahisi*, Vol.21, No.1, pp. 2-14, ISSN 1305-8282
- Matsumoto, A.K., Babul, N. & Ahdieh, H. (2005). Oxymorphone Extended-Release Tablets Relieve Moderate to Severe Pain and Improve Physical Function in Osteoarthritis: Results of a Randomized, Double-Blind, Placebo- and Active-Controlled Phase III Trial. *Pain Medicine*, Vol.6, No.5, pp. 357-366, ISSN 1526-2375
- McAlindon, T.E., LaValley, M.P., Gulin, J.P. & Felson, D.T. (2000). Glucosamine and Chondroitin for Treatment of Osteoarthritis: a Systematic Quality Assessment and Meta-Analysis. *JAMA: The Journal of the American Medical Association*, Vol.283, No.11, pp. 1469-1475, ISSN 0098-7484
- McGettigan, P. & Henry, D. (2006). Cardiovascular Risk and Inhibition of Cyclooxygenase: a Systematic Review of the Observational Studies of Selective and Nonselective Inhibitors of Cyclooxygenase 2. *JAMA: The Journal of the American Medical Association*, Vol.296, No.13, pp. 1633-1644, ISSN 0098-7484
- McHughes, M. & Lipman, A.G. (2006). Managing Osteoarthritis Pain When Your Patient Fails Simple Analgesics and NSAIDs and Is Not a Candidate for Surgery. *Current Rheumatology Reports*, Vol.8, No.1, pp. 22-29, ISSN 1523-3774
- McNair, P.J., Simmonds, M.A., Boocock, M.G. & Larmer, P.J. (2009). Exercise Therapy for the Management of Osteoarthritis of the Hip Joint: a Systematic Review. *Arthritis Research & Therapy*, Vol.11, No.3, p. R98, ISSN 1478-6354
- Messier, S.P. (2008). Obesity and Osteoarthritis: Disease Genesis and Nonpharmacologic Weight Management. *Rheumatic Diseases Clinics of North America*, Vol.34, No.3, pp. 713-729, ISSN 0889-857X
- Messier, S.P., Loeser, R.F., Miller, G.D., Morgan, T.M., Rejeski, W.J., Sevick, M.A., Ettinger, W.H., Jr., Pahor, M. & Williamson, J.D. (2004). Exercise and Dietary Weight Loss in Overweight and Obese Older Adults With Knee Osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis and Rheumatism*, Vol.50, No.5, pp. 1501-1510, ISSN 0004-3591
- Michael, J.W., Schluter-Brust, K.U. & Eysel, P. (2010). The Epidemiology, Etiology, Diagnosis, and Treatment of Osteoarthritis of the Knee. *Deutsches Arzteblatt International*, Vol.107, No.9, pp. 152-162
- Najm, W.I., Reinsch, S., Hoehler, F., Tobis, J.S. & Harvey, P.W. (2004). S-Adenosyl Methionine (SAME) Versus Celecoxib for the Treatment of Osteoarthritis Symptoms: a Double-Blind Cross-Over Trial. [ISRCTN36233495]. *BMC Musculoskeletal Disorders*, Vol.5, p. 6
- Neustadt, D.H. (2006). Intra-Articular Injections for Osteoarthritis of the Knee. *Cleveland Clinic Journal of Medicine*, Vol.73, No.10, pp. 897-4, 906, ISSN 0891-1150
- Nuesch, E., Rutjes, A.W., Husni, E., Welch, V. & Juni, P. (2009). Oral or Transdermal Opioids for Osteoarthritis of the Knee or Hip. *Cochrane Database of Systemic Reviews*, No.4, p. CD003115

- Nussmeier, N.A., Whelton, A.A., Brown, M.T., Langford, R.M., Hoeft, A., Parlow, J.L., Boyce, S.W. & Verburg, K.M. (2005). Complications of the COX-2 Inhibitors Parecoxib and Valdecoxib After Cardiac Surgery. *New England Journal of Medicine*, Vol.352, No.11, pp. 1081-1091, ISSN 0028-4793
- Pavelka, K., Gatterova, J., Olejarova, M., Machacek, S., Giacovelli, G. & Rovati, L.C. (2002). Glucosamine Sulfate Use and Delay of Progression of Knee Osteoarthritis: a 3-Year, Randomized, Placebo-Controlled, Double-Blind Study. *Archives of Internal Medicine*, Vol.162, No.18, pp. 2113-2123, ISSN 0003-9926
- Petrella, R.J. (2000). Is Exercise Effective Treatment for Osteoarthritis of the Knee? *British Journal of Sports Medicine*, Vol.34, No.5, pp. 326-331, ISSN 0306-3674
- Pham, K. & Hirschberg, R. (2005). Global Safety of Coxibs and NSAIDs. *Current Topics in Medicinal Chemistry*, Vol.5, No.5, pp. 465-473, ISSN 1568-0266
- Physical Activity Guidelines Advisory Committee. (2008). Physical Activity Guidelines Advisor Committee Report, 2008, 16.05.2011, Available from: <http://www.health.gov/PAGuidelines/Report/pdf/CommitteeReport.pdf>
- Puenpatom, R.A. & Victor, T.W. (2009). Increased Prevalence of Metabolic Syndrome in Individuals With Osteoarthritis: an Analysis of NHANES III Data. *Postgraduate Medicine*, Vol.121, No.6, pp. 9-20, ISSN 0032-5481
- Rahme, E., Pettitt, D. & LeLorier, J. (2002). Determinants and Sequelae Associated With Utilization of Acetaminophen Versus Traditional Nonsteroidal Antiinflammatory Drugs in an Elderly Population. *Arthritis and Rheumatism*, Vol.46, No.11, pp. 3046-3054, ISSN 0004-3591
- Reginster, J.Y., Deroisy, R., Rovati, L.C., Lee, R.L., Lejeune, E., Bruyere, O., Giacovelli, G., Henrotin, Y., Dacre, J.E. & Gossett, C. (2001). Long-Term Effects of Glucosamine Sulphate on Osteoarthritis Progression: a Randomised, Placebo-Controlled Clinical Trial. *Lancet*, Vol.357, No.9252, pp. 251-256, ISSN 0140-6736
- Reichenbach, S., Sterchi, R., Scherer, M., Trelle, S., Burgi, E., Burgi, U., Dieppe, P.A. & Juni, P. (2007). Meta-Analysis: Chondroitin for Osteoarthritis of the Knee or Hip. *Annals of Internal Medicine*, Vol.146, No.8, pp. 580-590, ISSN 0003-4819
- Rizkalla, G., Reiner, A., Bogoch, E. & Poole, A.R. (1992). Studies of the Articular Cartilage Proteoglycan Aggrecan in Health and Osteoarthritis. Evidence for Molecular Heterogeneity and Extensive Molecular Changes in Disease. *Journal of Clinical Investigation*, Vol.90, No.6, pp. 2268-2277, ISSN 0021-9738
- Rosenthal, M., Moore, P., Groves, E., Iwan, T., Schlosser, L.G., Dziewanowska, Z. & Negro-Vilar, A. (2007). Sleep Improves When Patients With Chronic OA Pain Are Managed With Morning Dosing of Once a Day Extended-Release Morphine Sulfate (AVINZA): Findings From a Pilot Study. *Journal of Opioid Management*, Vol.3, No.3, pp. 145-154, ISSN 1551-7489
- Roth, S.H., Fleischmann, R.M., Burch, F.X., Dietz, F., Bockow, B., Rapoport, R.J., Rutstein, J. & Lacouture, P.G. (2000). Around-the-Clock, Controlled-Release Oxycodone Therapy for Osteoarthritis-Related Pain: Placebo-Controlled Trial and Long-Term Evaluation. *Archives of Internal Medicine*, Vol.160, No.6, pp. 853-860, ISSN 0003-9926
- Sakalauskiene, G. & Jauniskiene, D. (2010). Osteoarthritis: Etiology, Epidemiology, Impact on the Individual and Society and the Main Principles of Management. *Medicina (Kaunas)*, Vol.46, No.11, pp. 790-797, ISSN 1010-660X

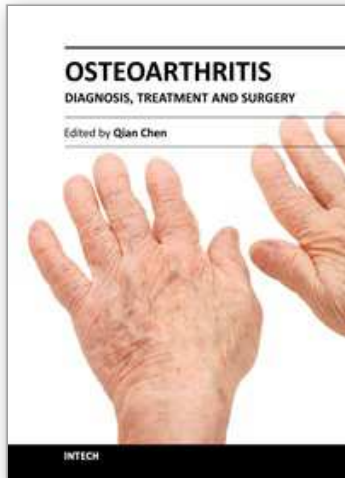
- Salaffi, F., Carotti, M., Stancati, A. & Grassi, W. (2005). Health-Related Quality of Life in Older Adults With Symptomatic Hip and Knee Osteoarthritis: a Comparison With Matched Healthy Controls. *Aging Clinical and Experimental Research*, Vol.17, No.4, pp. 255-263, ISSN 1594-0667
- Sander, O. (2003). Review: S-Adenosylmethionine Treats Osteoarthritis As Effectively As Nonsteroidal Anti-Inflammatory Drugs With Fewer Adverse Effects. *American College of Physicians Journal Club*, Vol.138, No.1, p. 21, ISSN 1056-8751
- Schjerning Olsen, A.M., Fosbol, E.L., Lindhardsen, J., Folke, F., Charlot, M., Selmer, C., Lamberts, M., Bjerring, O.J., Kober, L., Hansen, P.R., Torp-Pedersen, C. & Gislason, G.H. (2011). Duration of Treatment With Nonsteroidal Anti-Inflammatory Drugs and Impact on Risk of Death and Recurrent Myocardial Infarction in Patients With Prior Myocardial Infarction: a Nationwide Cohort Study. *Circulation*, Vol.123, No.20, pp. 2226-2235, ISSN 0009-7322
- Schroder, W., Tzschentke, T.M., Terlinden, R., De, V.J., Jahnel, U., Christoph, T. & Tallarida, R.J. (2011). Synergistic Interaction Between the Two Mechanisms of Action of Tapentadol in Analgesia. *Journal of Pharmacology and Experimental Therapeutics*, Vol.337, No.1, pp. 312-320, ISSN 0022-3565
- Segal, L., Day, S.E., Chapman, A.B. & Osborne, R.H. (2004). Can We Reduce Disease Burden From Osteoarthritis? *Medical Journal of Australia*, Vol.180, No.5 Suppl, p. S11-S17, ISSN 0025-729X
- Shane, A.A. & Loeser, R.F. (2010). Why Is Osteoarthritis an Age-Related Disease? *Best Pract Res Clin Rheumatol*, Vol.24, No.1, pp. 15-26, ISSN 1521-6942
- Solomon, S.D., McMurray, J.J., Pfeffer, M.A., Wittes, J., Fowler, R., Finn, P., Anderson, W.F., Zauber, A., Hawk, E. & Bertagnolli, M. (2005). Cardiovascular Risk Associated With Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention. *New England Journal of Medicine*, Vol.352, No.11, pp. 1071-1080, ISSN 0028-4793
- Sullivan, M.D., Bentley, S., Fan, M.Y. & Gardner, G. (2009). A Single-Blind, Placebo Run-in Study of Duloxetine for Activity-Limiting Osteoarthritis Pain. *Journal of Pain*, Vol.10, No.2, pp. 208-213, ISSN 1526-5900
- Sullivan, M.D., Edlund, M.J., Fan, M.Y., Devries, A., Brennan, B.J. & Martin, B.C. (2008). Trends in Use of Opioids for Non-Cancer Pain Conditions 2000-2005 in Commercial and Medicaid Insurance Plans: the TROUP Study. *Pain*, Vol.138, No.2, pp. 440-449, ISSN 0304-3959
- The National Collaborating Centre for Chronic Conditions. (2008). *Osteoarthritis: National Clinical Guideline for Care and Management in Adults*, Royal College of Physicians, London
- Towheed, T.E. & Anastassiades, T. (2007). Glucosamine Therapy for Osteoarthritis: an Update. *Journal of Rheumatology*, Vol.34, No.9, pp. 1787-1790, ISSN 0315-162X
- Towheed, T.E., Maxwell, L., Anastassiades, T.P., Shea, B., Houpt, J., Robinson, V., Hochberg, M.C. & Wells, G. (2005). Glucosamine Therapy for Treating Osteoarthritis. *Cochrane Database of Systemic Reviews*, No.2, p. CD002946
- Tsang, A., Von, K.M., Lee, S., Alonso, J., Karam, E., Angermeyer, M.C., Borges, G.L., Bromet, E.J., de, G.G., de, G.R., Gureje, O., Lepine, J.P., Haro, J.M., Levinson, D., Oakley Browne, M.A., Posada-Villa, J., Seedat, S. & Watanabe, M. (2008). Common Chronic Pain Conditions in Developed and Developing Countries: Gender and Age

- Differences and Comorbidity With Depression-Anxiety Disorders. *Journal of Pain*, Vol.9, No.10, pp. 883-891, ISSN 1526-5900
- Tzschentke, T.M., Christoph, T., Kögel, B., Schiene, K., Hennies, H.-H., Englberger, W., Haurand, M., Jahnel, U., Cremers, T.I., Friderichs, E. & De Vry, J. (2007). (-)-(1R,2R)-3-(3-Dimethylamino-1-Ethyl-2-Methyl-Propyl)-Phenol Hydrochloride (Tapentadol HCl): a Novel M-Opioid Receptor Agonist/Norepinephrine Reuptake Inhibitor With Broad-Spectrum Analgesic Properties. *Journal of Pharmacology and Experimental Therapeutics*, Vol.323, No.1, pp. 265-276, ISSN 0022-3565
- Tzschentke, T.M., De Vry, J., Terlinden, R., Hennies, H.H., Lange, C., Strassburger, W., Haurand, M., Kolb, J., Schneider, J., Buschmann, H., Finkam, M., Jahnel, U. & Friderichs, E. (2006). Tapentadol HCl. *Drugs of the Future*, Vol.31, No.12, pp. 1053-1061, ISSN 0377-8282
- US Food and Drug Administration. (2005). COX-2 Selective (Includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). April 7, 2005., 18.05.11 A.D., Available from:  
<http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm103420.htm>
- US Food and Drug Administration. (2010). Meeting of the Anesthetic and Life Support Drugs Advisory Committee (ALSDAC): Summary Minutes From the August 19, 2010 Meeting, 23.05.2011, Available from:  
<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM236241.pdf>
- Wagner, E. (2011). [Direct Costs of Osteoarthritis]. *Wiener Medizinische Wochenschrift*, Vol.161, No.1-2, pp. 44-52, ISSN 0043-5341
- Wandel, S., Juni, P., Tendal, B., Nuesch, E., Villiger, P.M., Welton, N.J., Reichenbach, S. & Trelle, S. (2010). Effects of Glucosamine, Chondroitin, or Placebo in Patients With Osteoarthritis of Hip or Knee: Network Meta-Analysis. *British Medical Journal*, Vol.341, p. c4675, ISSN 0959-8138
- White, A.G., Birnbaum, H.G., Buteau, S., Janagap, C. & Schein, J.R. (2007). Cost of Pain Therapy for Osteoarthritis in a Privately Insured Population in the United States. *Value in Health*, Vol.10, No.3, p. A117
- Wild, J.E., Grond, S., Kuperwasser, B., Gilbert, J., McCann, B., Lange, B., Steup, A., Häufel, T., Etropolski, M.S., Rauschkolb, C. & Lange, R. (2010). Long-Term Safety and Tolerability of Tapentadol Extended Release for the Management of Chronic Low Back Pain or Osteoarthritis Pain. *Pain Practice*, Vol.10, No.5, pp. 416-427, ISSN 1530-7085
- Woolf, C.J. (2011). Central Sensitization: Implications for the Diagnosis and Treatment of Pain. *Pain*, Vol.152, No.3 Suppl, pp. S2-15, ISSN 0304-3959
- Zhang, W., Doherty, M., Peat, G., Bierma-Zeinstra, M.A., Arden, N.K., Bresnihan, B., Herrero-Beaumont, G., Kirschner, S., Leeb, B.F., Lohmander, L.S., Mazieres, B., Pavelka, K., Punzi, L., So, A.K., Tuncer, T., Watt, I. & Bijlsma, J.W. (2010). EULAR Evidence-Based Recommendations for the Diagnosis of Knee Osteoarthritis. *Annals of the Rheumatic Diseases*, Vol.69, No.3, pp. 483-489, ISSN 0003-4967



- Zhang, W., Jones, A. & Doherty, M. (2004). Does Paracetamol (Acetaminophen) Reduce the Pain of Osteoarthritis? A Meta-Analysis of Randomised Controlled Trials. *Annals of the Rheumatic Diseases*, Vol.63, No.8, pp. 901-907, ISSN 0003-4967
- Zhang, W., Moskowitz, R.W., Nuki, G., Abramson, S., Altman, R.D., Arden, N., Bierma-Zeinstra, S., Brandt, K.D., Croft, P., Doherty, M., Dougados, M., Hochberg, M., Hunter, D.J., Kwok, K., Lohmander, L.S. & Tugwell, P. (2008). OARSI Recommendations for the Management of Hip and Knee Osteoarthritis, Part II: OARSI Evidence-Based, Expert Consensus Guidelines. *Osteoarthritis and Cartilage*, Vol.16, No.2, pp. 137-162, ISSN 1063-4584

IntechOpen



## **Osteoarthritis - Diagnosis, Treatment and Surgery**

Edited by Prof. Qian Chen

ISBN 978-953-51-0168-0

Hard cover, 404 pages

**Publisher** InTech

**Published online** 02, March, 2012

**Published in print edition** March, 2012

Osteoarthritis is one of the most debilitating diseases affecting millions of people worldwide. However, there is no FDA approved disease modifying drug specifically for OA. Surgery remains an effective last resort to restore the function of the joints. As the aging populations increase worldwide, the number of OA patients increases dramatically in recent years and is expected to increase in many years to come. This is a book that summarizes recent advance in OA diagnosis, treatment, and surgery. It includes wide ranging topics from the cutting edge gene therapy to alternative medicine. Such multifaceted approaches are necessary to develop novel and effective therapy to cure OA in the future. In this book, different surgical methods are described to restore the function of the joints. In addition, various treatment options are presented, mainly to reduce the pain and enhance the life quality of the OA patients.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Mila Etropolski (2012). Long-Term Treatment of Osteoarthritis Pain: Achieving a Balance Between Efficacy and Tolerability for a Successful Chronic Therapy, Osteoarthritis - Diagnosis, Treatment and Surgery, Prof. Qian Chen (Ed.), ISBN: 978-953-51-0168-0, InTech, Available from:

<http://www.intechopen.com/books/osteoarthritis-diagnosis-treatment-and-surgery/long-term-treatment-of-osteoarthritis-pain-achieving-a-balance-between-efficacy-and-tolerability-for>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2012 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen