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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; Klussmann 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 (Nuesch et al., 2009).

2.2.7 New treatment option: Tapentadol extended release, a μ-opioid receptor agonist and norepinephrine reuptake inhibitor

Tapentadol is a new, centrally acting analgesic that has μ-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 heath, 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-naive 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-naive 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).

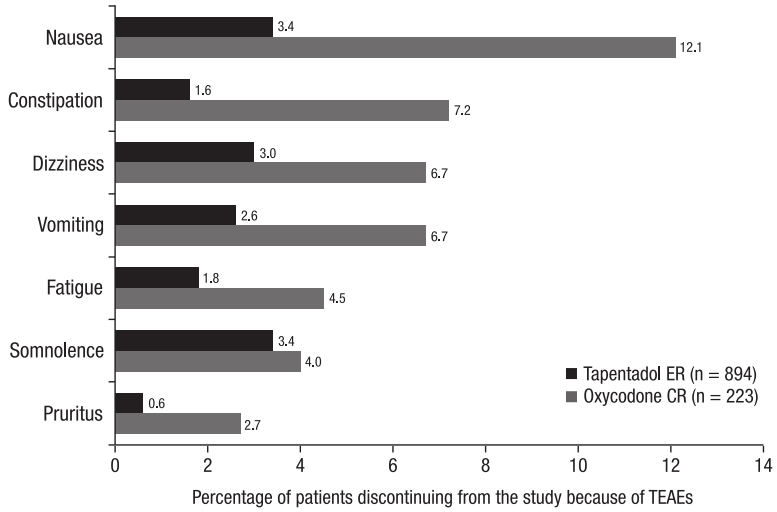

Fig. 1. TEAE-related discontinuations in a 1-year safety study of tapentadol ER (100-250 mg bid) compared with oxycodone HCl CR (20-50 mg bid). Reprinted from Pain Practice, Vol 10, Wild JE, et al, Long-term safety and tolerability of tapentadol extended release for the management of chronic low back 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; Klussmann 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 μ-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 μ-opioid analgesics in patients with moderate to severe, chronic osteoarthritis pain.

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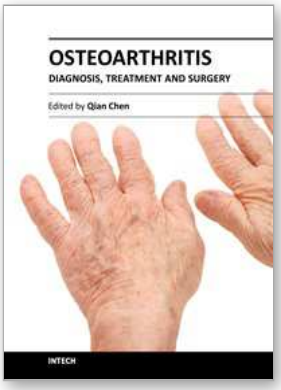

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Osteoarthritis is one of the most debilitating diseases affecting millions of people worldwide. However, there is no FDA approved disease modifying drug specifically for OA. Surgery remains an effective last resort to restore the function of the joints. 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.

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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