INTRODUCTION

Current approaches for the treatment of knee osteoarthritis (OA) are mainly symptomatic [1]. The target in treating patients with OA should be the safest possible intervention, with the best pain relief and prevention of further functional disability [2]. Better understanding of the pathophysiology of the disease will lead to emergence of novel therapies in the future [3]. There are two types of OA: primary, due to unknown cause, and secondary as occurs with trauma or other rheumatic, endocrine, metabolic, and congenital disorders [4]. Risk factors for knee OA include both non-modifiable risk factors such as, genetic predisposition, female gender, and age (> 50 years), and modifiable risk factors like obesity, recurrent trauma, and sedentary lifestyle [5]. The clinical picture emerges with worsening pain, morning stiffness of less than half an hour duration, swelling, and limited range of motion in the affected joint [6]. Physical exam reveals crepitus (especially over the knees), joint tenderness, effusion, and joint deformities in advanced stages. In addition, limited active and passive range of motion occurs. The diagnosis of knee OA is mainly a clinical one. It is also important to assess for depression, which can result from chronic untreated pain, and affects patients with OA quite regularly [7]. When present, depression must be acknowledged and addressed for the optimal management of OA. Various radiographic modalities are used to evaluate the severity of the joint involved. Plain radiography is the most practical, affordable, and available. Magnetic resonance imaging (MRI), however, is the most useful for demonstrating cartilage and joint structure damage and detecting early changes [8]. Despite excellent imaging techniques, radiological findings do not correlate well with the patients’ symptoms [9].

In this brief review, we will discuss treatment options for OA and provide supporting evidence behind the recommendations. One must acknowledge from the onset the difficulty in designing studies for this purpose. Measuring a subjective entity like pain, which fluctuates with disease, emotion, expectation, and personal experience, is challenging and requires large trials in order to mitigate individual and temporal variability. While radiographic studies may be used as a surrogate measure, the poor correlation with symptoms creates their own set of problems. For these reasons and others, the strength of the recommendations have been known to change over time, and are likely to do so in the future. Much of the recommendations in this review rely heavily on the most recent consensus statements from the European League Against Rheumatism (EULAR) [10], the Osteoarthritis Research Society International (OARSI) [11], the American College of Rheumatology (ACR) [12], and the trials on which they were based.

NON-PHARMACOLOGIC THERAPY

Weight reduction

Weight reduction decreases pain, improves physical activity, and has structural modifying effects on the knee cartilage. Early randomized controlled studies (RCT) showed a small but significant improvement in knee pain, stiffness, and function with weight loss [11]. In a more recent study by the Arthritis, Diet, and Activity Promotion Trial group (ADAPT), 76 obese or overweight inactive adults with knee OA were followed for 18 months, and their weight was documented. Subjects who achieved 10% weight loss had marked decrease in knee joint compressive loads during walking as compared to those with low or no weight loss [13]. Another trial showed that massive weight loss (20% body weight) induced by surgery in morbidly obese patients with knee OA not only improved pain and function, but also decreased inflammatory markers and had a structural effect on cartilage [14]. However, voluntary and involuntary weight loss in elderly patients leads to loss of muscle and bone mass resulting in an increased risk of falls and fractures. Weight reduction should be prescribed in the geriatric population with extreme caution and under expert guidance, and only for those who are obese (Body mass index [BMI] > 30 kg/m²). Despite these concerns, based on multiple randomized controlled trials (RCT), the OARSI gives weight reduction the highest level of recommendation with 100% consensus.

Exercise and assistive devices

Patients with OA usually avoid physical activity because of pain which eventually leads to muscle atrophy thereby increasing the stress on the knee joints [15]. Despite strong supporting evidence for the benefits of exercise on knee

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OA (level of evidence Ia, table I), physical activity unfortunately continues to be underutilized in clinical practice. In one survey, adults with OA were almost 50% more likely to be physically inactive compared to those without OA, which is not entirely surprising. However, in a meta-analysis of 13 RCTs, moderate but significant improvement in pain was shown with aerobic and knee strengthening exercises [16]. The choice of specific exercises, whether aerobic (isotonic), resistance (isometric), flexibility, range of motion, or aquatic should be individualized according to each patient’s needs and condition [16]. An exercise program is best guided by a trained physical therapist or adult sports medicine specialist rather than be self-guided. It is difficult to entirely tease apart exercise and weight loss, and most people will experience the benefit of both simultaneously. The combination of weight loss with physical exercises (as aerobic and quadriceps muscle strengthening) has been shown to decrease symptoms by strengthening the muscles of the knee [15]. Assistive devices can also decrease symptoms and improve function. There is widespread belief that a walking cane (in the contralateral hand) improves mobility and pain, but the strong recommendation supporting the use of walking aids is based on consensus rather than RCT. The level of evidence (LoE) for assistive devices at this time is IV and further trials are needed (Table I). On the other hand, in patients with varus or vulgus instability, a properly fitted knee brace can improve mobility and reduce pain, and decrease falls (LoE Ia).

**Other interventions**

Due to frustration with the limits and shortcomings of Western medicine in relieving arthritic pain, many patients have sought complementary and alternative interventions. Commonly used non-pharmacological treatments that have gained popularity in the past two decades are acupuncture, transcutaneous electric nerve stimulation (TENS), and tai chi [17]. Despite early anecdotal evidence of efficacy, few studies have investigated the role of alternative interventions in the management of knee OA. A trial that recently compared traditional Chinese acupuncture with sham acupuncture revealed that both have the same efficacy and the behavior of the acupuncturist plays a role in relieving the pain. Previous meta-analysis or RCT, however, showed significant improvement of chronic pain with acupuncture, which has earned it a level Ia evidence rating, but with low consensus agreement (Table II). The intrinsic difficulty in sham blinding, and the potential relaxing effect of the environment and operator may be the reason for inconsistent results. The role of transcutaneous electric nerve stimulation in treatment of knee OA is still debatable. A systematic review comparing TENS with sham versus no specific intervention was inconclusive [18]. TENS may be more effective for the management of low back pain and hip OA, but more trials are needed to further clarify its role in knee OA. tai chi is a traditional Chinese mind-body relaxation exercise aimed at decreasing pain, anxiety, and depression, and improving physical activity. It has rapidly gained popularity in Europe and the US over the past two decades due to the perceived multiple benefits. In fact, various clinical trials have shown improvement in psychological stress, pain, and physical activity [17]. Neither EULAR nor OARSI included tai chi among the interventions reviewed for recommendation, but there is general consensus that tai chi is a safe and effective intervention.

### PHARMACOLOGIC THERAPY

#### Acetaminophen

Acetaminophen, in doses under 4000 mg per day, is a safe and effective treatment for patients with mild-to-moderate OA of the knee. All three organizations, (EULAR, ACR, and OARSI) recommend acetaminophen as first-line treatment for osteoarthritis, and if effective, as the preferred long-term oral analgesic [19]. Acetaminophen has no significant anti-inflammatory activity. Among analgesics, it is generally viewed as the safest on gastric mucosa, blood pressure, and renal function. A recent study, however, showed that acetaminophen has an effect on both COX-1 and COX-2, which raises concern regarding long-term safety [20]. In fact, in recent years, both the safety and efficacy of long-term acetaminophen have been questioned. In a 2006 review of nearly 6000 subjects in 15 randomized controlled trials, acetaminophen showed a statistically significant but very small reduction in pain over placebo [21], raising the question of clinical efficacy. There was no significant difference in toxicity between acetaminophen and placebo in these short-term trials. However, possible renal and gastrointestinal toxicity occurs with long-term treatment, as shown in some, but not all, studies. In a case-control study using the UK General Practice Research Database [22], the relative risk for upper gastrointestinal (GI) bleeding or perforation was RR 3.6 (95% CI 2.60 to 5.10), but these findings were not replicated in a meta-analysis of three case-controlled trials (RR 1.2, CI 0.8-1.7) [23]. Similarly conflicting results were found for renal toxicity. In any case, acetaminophen is associated with less toxicity than other analgesic medications and remains the initial choice for treatment of knee OA. Acetaminophen is given the highest level of evidence (level Ia) by all agencies, with a strong recommendation and high consensus agreement [10-12].
Non-steroidal anti-inflammatory drugs (NSAIDs)
All orally administered NSAIDs, whether selective or non-selective, should be cautiously prescribed in elderly people due to their side effects on the kidneys, blood pressure (more so with COX-2 inhibitors), cardiovascular system, and GI tract. NSAIDs are more effective than acetaminophen in pain control, but in one study the effect size was minimal; side effects, on the other hand, are considerably higher.

Current guidelines recommend the use of NSAIDs at the lowest effective dose and caution against long-term use. In patients with increased GI risk, a selective COX-2 agent should be considered, or a non-selective NSAID with co-prescription for a proton pump inhibitor (PPI) or misoprostol for gastrointestinal protection. In fact, in elderly patients, a proton pump inhibitor should be prescribed with both selective and non-selective NSAIDs. Both non-selective and COX-2 selective agents should be used with caution in patients with cardiovascular disease. Naproxen is the preferred drug among the NSAIDs regarding cardiovascular safety [24]. A new drug, naproxcinod (nitronaproxen) is a derivative of naproxen with a nitroxybutyl ester which allows it to act as a nitric oxide donor. Naproxcinod is the first in this new class of drugs, the cyclooxygenase inhibiting nitric oxide donors (CINODs), and has the theoretical added benefit over naproxen of gastrointestinal and cardiovascular protection due to nitric oxide release. Over a one-year trial period, this drug showed similar analgesic efficacy compared to naproxen, and less gastrointestinal and blood pressure effects, but without reaching statistical significance [25].

Opioids
Opioids can safely be used in the elderly provided proper guidelines are followed. Opioids are usually indicated in moderate-to-severe pain when NSAIDs are ineffective or contraindicated. Opioid abuse or misuse should be considered when prescribing it to elderly patients despite the low risk of this overstated concern. Most opioids are metabolized in the liver by the cytochrome P-450 enzymes and have an associated risk of drug-drug interactions. Renal function should be monitored since opioid metabolites, which may be bioactive themselves, are cleared by the kidneys. In addition, other known adverse effects of opioids as constipation, nausea, and excessive sedation should be anticipated and addressed [26]. Many physicians and patients continue to be apprehensive about the use of opioids, particularly in the elderly, resulting in this class of drug being underutilized. The efficacy and safety profile of opioids, when used properly, is matched by few other analgesics, and clinicians should have a low threshold for starting opioids in moderate-severe pain. Weak opioids, such as codeine, are recommended by the World Health Organization (WHO) for early use in the progression of pain, and are often combined with acetaminophen for enhanced efficacy [27]. It is noteworthy to mention that in a recent randomized controlled trial, Tramadol was shown to have a similar efficacy to sustained release diclofenac in patients with knee or hip OA, and with a more favorable safety profile [28]. Tramadol is a centrally acting analgesic with knee or hip OA, and with a more favorable safety profile [29].

Glucosamine and chondroitin
Glucosamine is an endogenously synthesized hexosamine involved in the formation of hyaluronic acid, proteoglycans, glycolipids, and glycoproteins which are important constituents of articular cartilage. Chondroitin sulfate is a structural part of the extracellular matrix which is essential for pressure resistance through retaining water within the cartilage. The European League Against Rheumatism (EULAR) has given both glucosamine sulfate and chondroitin sulfate the highest level of evidence and recommendation strength [10]. Many clinical trials have shown marked symptomatic improvement with glucosamine sulfate compared to placebo or NSAIDs, as well as better tolerability and sustained effect, while others have shown no significant difference between placebo and glucosamine [29-30]. A recent randomized controlled pilot study using magnetic resonance imaging (MRI) in patients with OA of the knee showed a significant reduction in cartilage loss as early as six months in patients taking chondroitin sulfate [31]. The most recent Cochrane review of 4963 patients with OA taking glucosamine included 25 randomized controlled trials and showed a 22% improvement in pain and an 11% improvement in function using the Lequesne Index [32]. Glucosamine was shown to be better than placebo in patients using the Rotta glucosamine crystalline preparation, but not with other preparations [32]. In most studies, 1500 mg of glucosamine and 1200 mg of chondroitin sulfate was used daily. The effects are generally apparent.
2-3 weeks after starting treatment, and persist for a prolonged period [33]. If no response is noted within six months, treatment should be discontinued. The Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) was the largest multicenter, randomized, placebo-controlled study which showed some efficacy in combining both glucosamine and chondroitin sulfate for people with moderate to severe knee OA [34]. Despite the clinical benefit and the structural modifying effects from combining glucosamine and chondroitin sulfate that the GAIT and other trials have shown [35], limited data exist concerning their long-term safety. Concerns such as hyperglycemia with glucosamine or bovine spongiform encephalopathy in patients taking chondroitin sulfate (can be derived from animal sources) were unfounded. Caution should be taken when prescribing the combination to patients on warfarin because of the risk of increased INR and bleeding [36].

Glucosamine and chondroitin sulfate are classified as dietary supplements in the US and therefore not regulated by the Food and Drug Administration (FDA). Consequently, they cannot be marketed for the treatment of any specific disease, and safety and consistency of formulation are the sole responsibility of the manufacturer. In most of Europe, both compounds are sold as medical drugs, and are under strict regulation. European formulations, hence, eliminate the uncertainty that hangs over unregulated drugs.

**Omega-3 polyunsaturated fatty acids**

Omega-3 polyunsaturated fatty acids (ω-3 PUFA) are known for their anti-inflammatory actions and effect on increasing collagen synthesis. The main dietary source of ω-3 PUFA is fish, walnut, and flaxseed. The cardiovascular benefit of PUFA is well known, but only recently has the effect on OA been investigated. In a recent randomized study of 177 patients suffering from moderate to severe knee osteoarthritis, ω-3 PUFA was found to have a synergistic effect with glucosamine on pain relief when compared to glucosamine alone [37]. Other studies have shown the benefits of ω-3 PUFA on OA. In 2011, a study performed on an experimental model of OA to assess the net effect of ω-3 PUFA showed clear benefits in decreasing signs of OA [38]. Consensus recommendations at this time are to increase dietary intake of ω-3 PUFA from natural sources, or as supplements if necessary.

**Hyaluronic acid**

Hyaluronic acid (HA) is a glycosaminoglycan distributed widely throughout the body. It is a natural component of cartilage extracellular matrix and may contribute to cell proliferation. Hyaluronic acid is given as an intra-articular injection, and increases synovial fluid viscosity and elasticity. It is safe and well tolerated but relatively expensive. High molecular weight HA has a delayed onset but prolonged effect (up to 3-6 months), and is given once every 3-5 weeks. Many studies, but not all, show that HA can decrease pain and improves physical activity [39]. HA is recommended for use by ACR and EULAR when other measures of pharmacologic therapy fail. Because the efficacy of HA has been shown in randomized controlled trials, it is given a LoE rating of Ia. However, because of cost effectiveness, inconsistent benefit, and risk/benefit analysis, it is recommended as a last alternative before surgery.

**Intra-articular steroids**

Both ACR and EULAR have recommended intra-articular steroid injection in the treatment of local active joint inflammation and swelling. Intra-articular steroids have a rapid onset of action (few days) and an effect that last for a relatively short duration (3-4 weeks), in contrast to HA which has a more delayed onset of action and more prolonged effect. Intra-articular steroid injections showed better pain relief with no functional improvement according to most studies in literature [40]. For obvious reasons, this treatment option should not be used for the primary management of OA, but can be a useful adjuvant treatment when additional relief is urgently needed. Due to the clinical evidence of efficacy but short duration of pain relief and inconvenience, intra-articular steroid injections are given a high LoE but weak recommendation.

**Other applications and new therapies**

Duloxetine (Cymbalta), a serotonin-norepinephrin reuptake inhibitor (SNRI) has shown efficacy in treating pain in knee OA according to a randomized controlled study of 256 subjects [41]. At 13 weeks follow-up, treatment with duloxetine was associated with significant pain reduction and functional improvement, but also with significant side effects and dropout rate [41]. Furthermore, it is not entirely clear how much of the benefit was due to inadvertent treatment of concomitant depression. Topical NSAIDs and capsaicin (a chili pepper extract) have been shown to be effective adjuvant or alternative treatments for knee OA in RCTs and meta-analysis of these trials [11], though the size of the effect has been debated. Topical NSAIDs do not display the serious side effects of their oral counterpart, and have been used in Europe for decades. Diclofenac 1% gel (Voltaren) delivers effective concentrations in the affected joint but with limited systemic exposure. However, local reactions such as burning, itching, and rash are not uncommon, especially with capsaicin. A newly developed therapy for OA is tanezumab, the first monoclonal antibody that inhibits nerve growth factor. Tanezumab showed great improvement in pain and physical activity, but unfortunately was withheld by the FDA because of increased number of joint replacements in patients receiving this medication [42].

**SURGICAL AND OTHER RECOMMENDATIONS**

When nonsurgical measures fail to achieve adequate pain relief, or when there is marked limitation of daily activities, surgical options must be considered.

Based on individual criteria, several surgical procedures can be performed, including arthroscopic debridement, osteotomy, unicompartmental knee replacement, patellofemoral replacement, total knee replacement, and
joint fusion. With total knee arthroplasty, pain scores improved more rapidly and completely than does physical function. For optimal results, patients with OA should be referred for surgical care prior to the onset of joint contracture, severe muscle atrophy, or advanced joint deformity. Total knee replacement generally is less effective in restoring patients to normal function when compared to hip replacement surgery. More severe pain, functional limitation, frailty, mental distress, and co-morbid conditions are associated with poor surgical outcome. Ten to twenty percent of patients who undergo total knee replacement are dissatisfied with the result [43].

SUMMARY

Osteoarthritis is the most common form of arthritis, and its incidence increases rapidly with age. Osteoarthritis is a progressive degenerative disease, and treatment must evolve with disease progression. Several classes of medications and treatment modalities have been used to relieve pain and preserve function. Most have been studied extensively but results of even well-designed trials can diverge. Furthermore, effect of a drug (beneficial or adverse) in an individual patient is not always predictable and may differ from the class effect. A short treatment trial may be necessary to determine efficacy. This potential discrepancy between statistical outcome and individual result is captured in the guidelines, to whatever extent possible. A summary of recommendations for select interventions compiled from multiple guidelines is presented in table II.

In closing, interpretation of guideline recommendations, and how they were derived, must be clarified, since they have been a source of confusion and misinterpretation. Level of evidence (LoE) refers to the source from which the evidence was derived. It describes the quality of evidence and academic vigor, with meta-analysis of RCT being of strongest quality and expert opinion the lowest. The strength of effect describes how much of a clinical effect (usually benefit) is expected from the intervention. The strength of recommendation incorporates LoE and strength of effect, as well as cost, safety, and feasibility. An intervention with a high LoE does not necessarily trigger a strong recommendation. For example, NSAIDs have a greater effect on pain reduction than acetaminophen in most studies, but carries a lower recommendation due to concerns with long-term safety. Total knee arthroplasty has a LoE of III since no blinded RCT have studied the procedure, yet it carries a strong recommendation in advanced OA. In the five years between the publication of the EULAR and the OARIS guidelines (2003-2008), new studies were published explaining, in part, the difference in recommendations among the agencies. Future guidelines will undoubtedly evolve further.

ADDENDUM

As this issue of the LMJ went to print, the 2012 guidelines of the American College of Rheumatology were published [44]. They recommend aerobic and aquatic exercises and decreasing body weight as a part of non-pharmacologic management of knee OA. Acetaminophen, oral or topical NSAIDs, Tamadol and intra-articular corticosteroid injections are recommended as needed. On the other hand, they recommend against the use of chondroitin sulfate, glucosamine, and topical capsaicin, and made no mention of duloxetine, hyaluronic acid, or opioid analgesics. The full report can be accessed online [44].

REFERENCES