Editorial

Opioid Therapy for Osteoarthritis of the Hip and Knee: Use It or Lose It?

Osteoarthritis (OA) is a painful condition whose prevalence will increase as the population ages globally[1]. The American College of Rheumatology (ACR) defines OA as a "heterogeneous group of conditions that lead to joint symptoms and signs that are associated with defective integrity of articular cartilage in addition to related changes in the underlying bone at the joint margins."[2] Patients, however, seek medical attention due to joint pain and loss of function[3].

Prevalence rates for hip and knee OA depend on whether the diagnosis is made radiographically or clinically[4]. The most comprehensive survey, from the Netherlands[5], reveals that radiographic prevalence among adults aged 45–54 was 13 per 100 for knees, and 2.5 per 100 hips. For the age group 65–74, this rose to 28 per 100 knees and 10 per 100 hips. There is often discordance between radiographs and reports of joint pain[3,6]. Ten percent of those with normal radiographs report pain, while only 40–79% of those with advanced radiographic abnormalities report pain[3]. Importantly, though, pain is a better predictor of disability than radiographic grade[7]. In the Johnson County Osteoarthritis Project, 35.6% of subjects over age 45 reported moderate/severe knee pain in the last 30 days, with 11.6% reporting mild pain[7]. The US National Survey of Self-care and Aging in 38 urban and 12 rural areas addressed arthritis disability. Interviews and telephone followup in a random sample aged 65 and older showed 48% had daily arthritis pain, 32.8% were kept from sleeping, and 43.1% reduced their usual daily activities[8]. A recent update of this project also documented reduced health related quality of life[9]. A population based, random stratified sampling in northeast Scotland showed that 50% of the population had chronic pain. Over the age of 75, 62% of the sample reported chronic pain[10]. Arthritis was the principal reason cited, and was noted in 13.7% of males, 17.8% of females, and 28.1% of those over age 75 years. Nearly 16% of this population reported severe, disabling pain on the von Korff pain grading system[11]. Thus OA of the hip and knee is an important public health problem, and it is relevant to ask what role potent pain medications, i.e., opioids, may have in its management.

What are the pain generators in hip and knee OA? These might include the joint capsule, ligaments and insertions, periosteum and subchondral bone, and the synovium[3,12]. The exact pain source is often unclear in any individual. There are, however, opioid receptors in inflamed OA synovium[13].

The American Geriatric Society (AGS) emphasizes the impact of chronic pain in older adults[14]. They report 18% of older Americans take analgesics more often than weekly, with musculoskeletal pain a common cause. The AGS suggests pain consequences are depression, decreased socialization, poor sleep, poor ambulation, and increased health care use. They further state, "for many patients chronic opioid therapy may have fewer life threatening risks than the longterm daily use of NSAID" and "patients should not be overburdened with opiophobia."

Osteoarthritis guidelines provide limited guidance on opioid use. The 1995 ACR guidelines for hip OA suggest opioids be avoided for longterm use, but short term use may be helpful, without reference to primary data[15]. The 1995 ACR knee OA guidelines do not discuss opioids directly[16]. The 2000 update of the ACR OA guidelines suggests that opioids might be used as a medication of last resort[17]. The 1998 UK guidelines on degenerative arthritis suggest that if relief is inadequate with 2.4 grams of ibuprofen and 4.0 grams of paracetamol a day, other antiinflammatories or opioids may be considered[18].

There are many reasons physicians are reluctant to consider opioids[19,20]. These include: a perception that pain and suffering are an inevitable part of life; a fear of opioid side effects, including addiction; political and social pressures to control illicit drug use; and lack of knowledge about opioid efficacy in OA. Each of these concerns will be examined.

Pain and suffering are related, but different, components of the pain experience[21]. Suffering is a cognitive experience, not merely the perception of pain. It is pain and its associated impact on the psyche. An artificial mind-body split was originally proposed by Descartes to separate science, the study of the physical world, from the psyche, the exclusive domain of the Church, to allow for human scientific experimentation. This 200-year-old dichotomy lingers in the erroneous belief that suffering is a spiritual, not medical event, outside the realm of medical practice. Yet the public clearly views pain management as a medical priority[22]. A leading

bioethicist argues: "to leave a person in avoidable pain and suffering should be regarded as a serious breach of fundamental human rights."[23]

Tolerance, the need for a higher dose of a drug to achieve the same pharmacologic effect, is not synonymous with addiction[24]. Tolerance appears related to a modulation in receptor numbers and their binding capacity, in response to chronic drug administration. Tolerance occurs with many drugs, including nitrate therapy[25].

Dependence is the presence of unwelcome effects upon drug withdrawal, and is also not equivalent to addiction. Withdrawal symptoms for opioids are characterized by increased adrenergic hyperactivity, and include excitability, nervousness, sweating, and diarrhea.

Addiction is abnormal drug seeking behavior[24]. It is characterized by an unwillingness to taper a medication when an alternative treatment is offered; reports of no relief with non-opioid alternatives; a strong preference for short acting forms or bolus medications; obtaining multiple prescriptions from multiple sources; and by the use of street drugs. Addiction is the continued used of a drug in spite of negative personal, economic, or social consequences of the drug's use.

Addiction is rare among individuals who truly have pain[14,26-28]. The Boston Collaborative Drug Study evaluated many types of drug use and side effects in hospitalized patients[26]. They reviewed over 10,000 prescriptions for opioids. Abnormal drug seeking behavior was found in only 2 cases (0.04%) of hospitalized patients. Ytterberg and colleagues at the University of Minnesota studied patients with rheumatoid arthritis, OA, and other rheumatic problems for addictive behaviors[27]. OA patients were the largest group of opioid users. The study found 4 of 800 patients (0.2%) had abnormal opioid behavior when followed 3 years through pharmacy records. There were no obvious predictors of drug seeking, but unresolved psychosocial problems were noted as a cautionary factor.

OA patients stop opioids when their pain is relieved by other means. In a study of opioid use before and after definitive orthopedic management of hip or knee OA, patients stopped opioids when their pain improved[28]. While 39% of patients took opioids preoperatively, only 1.9% did postoperatively, with a parallel decline in pain scores from 4.9/6.0 to 1.8/6.0.

The American Geriatric Society notes that "those 60 years of age and older account for less than 1% of participants attending methadone maintenance programs."[14]

While it is certain that some prescription opioids end up on the streets, the exact magnitude of this problem appears to be small[29]. A recent ecological study showed that even as the number of prescriptions for opioids was rising, the number of opioid related admissions to emergency departments was declining[30]. Most of these admissions were in younger males, a different demographic profile from the OA patient population.

The euphoric experience addicts seek from opioids is not equivalent across all drugs, and is based on different actions on the mu (μ), kappa (κ), and sigma (σ) receptors. The mu receptor is mostly responsible for opioid analgesic effects, while the sigma receptor is responsible for the hallucinogenic and excitatory effects of opioids. Methadone, as a relatively pure mu receptor agonist, does not give the euphoria of other opioids[31].

Respiratory depression is a function of blockade of the mu receptor, and occurs early in the use of the drug. Tolerance rapidly develops within days[32].

Opioids do cause minor changes in neurological function, especially in body sway[33]. In a controlled study, patients who required regular medications for control of malignant disease were compared to individuals with malignant disease who did not. A detectable difference in body sway was noted. The clinical significance of this slight sway was unclear to the authors. These authors also reported that a 30% increase in any stable dose is sufficient to overcome any tolerance that had developed. Codeine and propoxyphene have been shown to increase the risk of hip fracture in those over age 65[34]. The risk declines with continued use, but does not return to baseline. However, lower limb arthritis is also a risk factor for falls[35]. The relative contribution of both disease and drugs to falls in the elderly is not entirely clear.

Nausea, vomiting, and diarrhea are common opioid side effects. The randomized trials shown in Table 1 suggest their occurrence in 25% to 66% of subjects, leading to dropout in 10% to 25% of subjects. These nuisance side effects may be managed with slow dose titration. Tolerance frequently develops to these nuisance side effects with continued use[36]. It is important to note that there is no evidence that longterm opioid use creates any irreversible physical changes in any organ system[32].

Efficacy is best evaluated using the randomized clinical trial design. To judge the potential benefits of opioids in the treatment of OA of the hip and knee, primary studies were sought using Internet Grateful Med V2.6.3. A search was conducted from 1996 to March 2000 using the MeSH headings "osteoarthritis and narcotics" without language restriction. The reference lists from the trials and review articles identified were reviewed. Trials were included if they studied hip or knee OA primarily, but excluded if they focused primarily on back OA or back pain. These 15 trials are summarized in Table 1.

A variety of opioids have been studied, including codeine, dextropropoxyphene, dihydrocodeine, meptazinol, oxycodone, pentazocine, tilidine-naloxone, and tramadol. All published trials do demonstrate superiority of the opioids compared to placebo[36-41]. When acetaminophen (paracetamol) is used as a comparator or rescue medication, opioids are superior analgesics[40,42]. These trials also suggest that opioids are superior to nonsteroidal antiinflammatory

Table 1. Opioid trials.

Author	Patients Enrolled	Treatments	Enrolled, Completed, Duration	Outcomes	Results	Side Effects
Brooks, *et al,* 1982	OA and RA	Background NSAID & dextropropoxyphene 32.5 mg	12 OA patients, 12 completed, a single dose	1. Pain 10 cm VAS @ 1–4 h 2. 10 cm VAS pain relief	Dextropropoxyphene better than placebo	Equivalent side effects. Nausea and headaches mostly.
Kjaersgaard-Anderson, 1990	OA hip	Paracetamol 3.0 g vs codeine 240 mg + paracetamol 3.0 mg	161, 97 completed, 4 weeks	1. Pain: AM, evening, week (5 pt Likert) 2. Patient global (5 pt Likert) 3. Rescue ibuprofen	41% better on combo 20% on paracetamol @ 1 week. Less ibuprofen rescue codeine @ 1 wk. Codeine favored	52% dropout rate on codeine, 38% on paracetamol. SE nausea, dizzy, vomit, constip common, early.
Boissier, 1992	OA knee or hip	Paracetamol 2.4 g + dextropropoxyphene 180 mg vs paracetamol 3.0 g + codeine 180 mg	141, 59 completed, 42 days ITT analysis	1. Acceptability (4 pt Likert) 2. Pain (10 cm VAS) 3. Function (4 pt Likert) 4. MD global (4 pt Likert) 5. Patient global (4 pt)	No difference in efficacy for completers. 53% "fail" codeine vs 29% dextropropoxyphene	27/71 drop on codeine vs 9/70 on dextropropoxy. SE in 51/71 on codeine 58/70 vs dextropropoxyphene
Lloyd, *et al,* 1992	OA hip	Dihydrocodeine 60 mg 2–4 tabs/day vs paracetamol 325 mg + dextropropoxyphene 32.5 mg 6–8 tabs/day	86, 57 completed, 2 weeks ITT analysis	1. Daily pain (10 cm VAS) 2. Night pain (yes/no) 3. Pain with motion (4 pt Likert)	Both groups improved over baseline. No difference between groups.	17 dihydocodeine, withdraw vs 4 on dextropropoxyphene SE in 28/43 dihydrocodeine vs 18/43 dextro. Nausea, vomit, constipation common
Van Cauwenberge, *et al,* 1992	OA hip or knee	Tilidine-naloxone vs pentazocine No doses specified. Up to 8 tabs/day	52, 50 completed, 14 days	1. Night, 2. Starting, 3. Resting, 4. Walking pain (3 pt scale) 5. MD swelling 6. Palpation pain 7. ROM exercises 8. MD & 9. Patient global 10. Starting pain (21 pt) 11. Night pain (21 pt)	Where differences exist, these favor tilidine-naloxone treatment	No SE leading to dropouts. SE 10/25 on tilidine-naloxone vs 7/25 on pentazocine. SE not described
Flavell-Matts, 1980	OA & RA OA number not given	Meptazinol 20 mg vs pentazocine 40 mg 4 caps/day	60, 51 completed, 1 week crossover (no washout)	1. Pain relief (3 pt Likert) 2. Drug preference	Trend to pentazocine preference not statistically significant. Pain relief not presented.	3 withdraw on pentazocine. SE 22% on meptazinol vs 31% on pentazocine. Mostly nausea, vomit, dizziness, vertigo.
Andrews, *et al,* 1976	OA unspecified	Paracetamol 500 mg + dihydrocodeine 10 mg. Maximum 8 tabs/day vs paracetamol 500 mg + pentazocine 15 mg. Max 8 tabs/day	55, 46 completed, 7 day crossover (no washout)	1. Pain severity (VAS) 2. Tablet effective (VAS) 3. Drug preference	Equivalent effectiveness. No preferences	No dropouts for SE on either comb. SE for 33% on pentazocine vs 48% on dihydrocodeine.
Vlok, *et al,* 1987	OA unspecified	Paracetamol 250 mg + ibuprofen 200 mg + codeine 10 mg 2–3 tablets/day vs ibuprofen 200 mg 3 tabs/day	31, 28 completed, 28 day crossover, 7 day washout	1. Pain (10 cm VAS) 2. Drug preference	Combination with codeine more effective vs ibuprofen alone, with 64% favor combination, 29% favor ibuprofen	1 dropout. Group not stated. SE 10/28 on codeine combo, 3/28 on ibuprofen. Nausea, constip more common on codeine.

Table 1. Continued

Author	Patients Enrolled	Treatments	Enrolled, Completed, Duration	Outcomes	Results	Side Effects
Fancourt, 1984	OA & RA OA not separated	Meptazinol 200 mg vs placebo. Up to 8 tabs/day	60, 47 have complete data, 3 days	1. Pain severity (3 pt) 2. Spontaneous pain. 3. Pain on pressure. 4. Pain expression. 5. MD global (10 cm VAS) 6. Patient pain intensity. 7. Patient pain (4 pt scale)	Pain measures favor meptazinol. MD and patients prefer meptazinol.	No SE dropouts. SE 50% on meptazinol vs 44% placebo. Nausea, vomiting, dizziness common.
Quiding, *et al,* 1992	Hip OA	Ibuprofen 200 mg + codeine 30 mg vs ibuprofen 200 mg vs placebo for 6 doses	27, 26 completed, 32 h crossover, 2 day washout	1. Pain intensity (10 cm VAS) 2. Patient preference 3. Rescue acetaminophen use.	Pain scores: codeine combo > ibuprofen > placebo. Patient preferences: 14 codeine, 11 ibuprofen, 1 placebo. Less rescue analgesia in codeine combo group	No dropouts for SE. Of 26 patients, 11 SE on codeine, 5 ibuprofen, 6 placebo. Nausea, constipation, dizziness common
Caldwell, *et al,* 1999	OA neck, back, knees	Stable NSAID 1 mo, then oxycodone CR 20 mg/day vs IR 5 mg + 325 mg acetaminophen qid vs placebo	167 start run in phase 1 month on oxycodone IR. 107 enter DB phase 71 completed, 30 days ITT analysis	1. Pain (4 pt Likert) 2. Sleep (5 pt Likert)	CR=IR for pain and sleep. Both CR and IR better than placebo on pain and sleep.	Discontinuation SE: 3 CR, 5 IR, 3 placebo. SE are less CR vs IR. SE are tiredness, constip, nausea, dry mouth, pruritis in 1/3 to 2/3 of patients.
Peloso, *et al,* 2000	OA hip and knee	Codeine contin vs placebo mean dose 160 mg bd	103, 66 completed, 4 week study, completer and ITT analysis	1. WOMAC subscales (pain, stiffness, function) 2. Pain intensity last week (VAS) 3. Sleep (4 pt Likert) 4. MD global (5 pt Likert) 5. Patient global (5 pt Likert) 6. Rescue acetaminophen use	All outcomes favor codeine (ITT & efficacy) Dose-response relationship apparent for pain and function. Less acetaminophen rescue in codeine group.	Discontinue for SE: 15/51 codeine, 4/52 placebo. SE rates; Constip (49, 11%) somnolent (39, 10%), dizzy (33, 8%) codeine vs placebo.
Roth, *et al,* 2000	OA 31% knee 46% spine	Placebo vs oxycodone CR 20 mg/day vs oxycodone CR 40 mg/day	133, 63 completed, 14 days + 3–9 mo longterm study	1. Mean daily pain intensity (0–3 Likert) 2. Activities and lifestyle questionnaire (1–4 Likert) 3. Brief pain inventory	Lack of effect: 22 on placebo, 12 at 10 mg dose, 5 at 20 mg. Mean pain intensity, sleep, mood better 20 mg vs 10 mg or placebo.	Discontinue for SE: 28/133 oxycodone. 65% report 1 side effect, mostly nausea, vomit, somnolence.
			Trials with Tramadol			
Roth, 1999	OA hip, knee, neck, back Hip and knee (n = 37)	Stable NSAID. 24 h run-in phase tramadol. Tramadol 50 mg caps vs placebo. Up to 8 per day.	63 enter 24 h run-in phase, 42 enter DB phase, post run-in phase. 23 completed, 13 day trial, time-to-event analysis (exit for lack of effect)	1. Time to exit 2. Pain at rest 3. Pain on motion 4. Current pain (4 pt scale) 5. Patient global 6. MD global	Fewer exit on tramadol vs placebo: 16 vs 46%. Reduced rest pain, pain on motion, and better patient & MD global on tramadol vs placebo	Discontinue for SE: 6/21 tramadol vs 1/22 on placebo: Common side effects tramadol vs placebo: nausea (35, 14%), constip (45, 0%), drowsiness (25, 14%), vertigo, dizziness, light-headedness (40, 0%).
Schnitzer, *et al,* 2000	OA knee	Washout NSAID 1 week. Naproxen 250 1 week, responders out. Naproxen 500 bd 2 wks, with run-in tramadol 200 mg/day 1 week. Randomized to tramadol 200 mg/day vs placebo. Withdraw naproxen over next 1 mo	381 washout, 365 left on low dose naproxen 500/day 328 enter high dose naproxen 500 bd + tramadol 200 mg/day, 240 randomized to tramadol or placebo, 236 evaluable patients at 8 wks, ITT analysis	1. Minimum effective naproxen dose stratified by naproxen responders vs non-responders. 2. Pain currently (10 cm VAS)	Tramadol decreases need for naproxen in "naproxen sensitive" group. If non-responder to high dose naproxen, then tramadol no better vs placebo	Discontinue for SE on tramadol + naproxen: 19.3% in run-in phase. Common side effects tramadol + naproxen run in and DB phases: nausea (27.3%) dizziness (20.6%) somnolence (15.1%) headache (12.9%) vomiting (11.9%)

VAS: visual analog scale, ITT: intention to treat analysis, DB: double blind, > superior efficacy in comparison, IR: intermittent release, CR: controlled release, combo: combination treatment, SE: side effects, constip: constipation, pt: point, ROM: range of motion.

drugs (NSAID)[38,43], or lead to reduction in NSAID use[44]. These trials do not suggest important differences in efficacy between opioid comparators[45-50]. Equipotent doses of opioid therapy are rarely predefined in these trials, limiting the ability to judge true differences between them. In addition, the inconsistent application of outcome measures in these trials precludes metaanalysis.

Most of the studies are of short duration, with the longest double blind phase being 6 weeks taking opioids[46] and 8 weeks taking tramadol[44]. The mean duration of all trials combined is 19.4 days (SD 16.2 days, range 1 day to 8 weeks). It is important to note that both the open label portion of the Roth trial[36] and the data from the University of Minnesota[27] suggest that opioid benefits continue for 1 to 3 years.

While the exact role of opioids is best established using patient based utilities comparing risks and benefits of opioid with competing therapies[51], the published literature provides some basis for recommendations. There are several categories of OA patients who would seem appropriate for a trial of opioids. This includes those with moderate to severe OA pain, requiring medicinal therapies, where acetaminophen is insufficient, and for whom traditional NSAID or cyclooxygenase-2 (COX-2) specific inhibitors are contraindicated. An opioid trial may also be warranted when traditional NSAID or COX-2 specific inhibitors are not useful, or are insufficient on their own.

Opioids are effective in OA hip and knee pain, and have predictable side effects. It would be unwise were physicians to discount an entire class of medications over unfounded fears and incomplete knowledge of their benefits.

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