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Osteoarthritis (T Appleton, Section Editor)

# Opioids and Cannabinoids for Osteoarthritis: Either, Both, or Neither

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## Abstract

*Purpose of the review* Pain is a prevailing symptom in osteoarthritis (OA) and greatly impacts quality of life. Pain-relieving strategies over thousands of years have included opioids and cannabinoids but require critical evaluation of efficacy and risks in this twenty-first century. This review will examine the most up-to-date evidence for use of these two categories of drugs.

*Recent findings* Contrary to the previous concept that opioids would be advantageous for OA, the emerging evidence for true efficacy and overwhelming risks strongly supports recommendation against use. In contrast, cannabinoids, especially in the form of herbal cannabis, have been aggressively touted by advocacy, the media, and industry as an ideal and potentially less harmful panacea for many medical conditions, including relief of pain. There is currently absence of any sound study for effect of cannabinoids in management of pain associated with OA.

*Summary* In this era of uncertainty about cannabinoids, rheumatologists must exercise extreme caution in counseling patients and emphasize the potential but largely unknown risks for those with OA wishing to use cannabis. Therefore, at this time, opioids in particular, and likely also cannabinoids, should only be considered for the rare patient with severe OA where suffering is extreme and surgical options are unavailable or too high risk.

## Introduction

In this article, we will address pain management for patients with osteoarthritis (OA) with particular attention to the evidence for use of opioids and cannabinoids. OA is one of the most prevalent chronic diseases worldwide, with expectations that prevalence will increase dramatically in the coming decades [1, 2]. As OA is not curable and greatly impacts health-related quality of life (HrQoL), treatments are focused toward symptom relief. Pain, a prevailing symptom, is currently poorly managed and is associated with significant morbidity [3]. Analgesic treatment has been the cornerstone of OA pain management over decades but with knowledge that drugs offer mostly modest benefit and a high rate of side effects. Depending on the pattern of joint involvement, current therapies recommended in OA guidelines include acetaminophen, injectable corticosteroids, serotonin-norepinephrine reuptake inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids, with opioids as last line therapy. Nonetheless dispensing rates for high-dose formulations of several opioids, including morphine, hydromorphone, oxycodone, and fentanyl, have increased by 23% between 2006 and 2011 for the Canadian population [4•]. Similarly, long-term opioid use is reported for 8–26% of Medicare patients with OA in the USA [5]. With limited high-quality evidence for efficacy and concern about adverse effects, the door has opened for alternate treatments, with cannabinoids a prime contender. Promoted by advocacy, media, and tremendous public enthusiasm, physicians must be up to date with current evidence for cannabinoid use, risks, and cautions and must be prepared to effectively counsel patients. We will discuss the evidence concerning the use of both opioids and cannabis in OA, as well as potential risks with reference to the most recent publications in the literature.

# Prevalence of OA and impact on life

OA was estimated to affect 303 million individuals worldwide in 2017, a figure that is 60 million more than in 2013 [3, 6]. The poor HrQoL experienced by OA patients is illustrated by the observation that 19% of patients awaiting total hip replacements and 12% awaiting total knee replacement reported a state of health "worse than death" using the EuroQol five-dimension questionnaire [7]. Non-institutionalized adults with OA experience more pain interference with daily activities, functional limitation, and reduced HrQoL than those without OA, with adjusted incremental annual total healthcare costs and lost wages estimated as a national excess cost of $45 billion and $1.7 billion, respectively [8]. OA is associated with more comorbidity (metabolic syndrome, peptic ulcer disease, stroke) than those without OA, with prevalence rates for any comorbidity reported as 67% (95% CI:57%–74%) versus 56% (95% CI:44%–68%), respectively [9]. Eleven percent of Japanese OA patients had depression, which reduced HrQoL and increased healthcare costs [10]. The staggering prevalence of OA, associated comorbidity, and far-reaching health-related consequences emphasize the need for effective symptomatic treatments pending discovery of a cure.

# Pain of OA

Understanding of OA pain mechanisms has evolved in recent years. OA pain is not only nociceptive due to local tissue damage but also has a prominent neuropathic component with more widespread neuropathic changes distant from the anatomical site reported in up to 20% of patients [11, 12]. This central sensitization results in reduced pain threshold at sites distant from the OA lesion

and predisposes to generalized heightened pain sensitivity. Central sensitization, which presents as chronic widespread pain, has consequences for global well-being and can even adversely affect surgical outcomes [13]. Radiographic changes are poorly correlated with OA symptoms, with bone marrow lesions observed on magnetic resonance imaging showing better association with pain [12]. In addition, the pain experience is modulated by other factors such as previous pain experience, comorbidities, and psychosocial milieu, all contributing to the biopsychosocial model of pain [10]. This complexity of OA pain mechanisms likely contributes to the poor response to standard treatments.

OA pain is described as dull and aching, aggravated by activity and mostly improved with rest. Pain can also be present at rest and can interfere with sleep. OA pain can fluctuate with periods of exacerbation identified as flares, due to mechanical changes within the joint or be induced by inflammation [14, 15]. Accelerated OA is newly recognized as a rapid joint destruction of mostly weight bearing joints and associated with more pain and an earlier need for joint replacement [16].

## Therapies for pain reduction in OA

Any treatment approach for OA pain must begin with non-pharmacologic measures which will be addressed by other authors in this journal edition. Disease-modifying treatments have to date been unsuccessful, with symptom relief the current focus of management. Corticosteroid injections can improve pain, but their usefulness can be limited in polyarticular involvement. In addition, there are theoretical concerns of accelerated cartilage destruction following repeated injections, but they have not been demonstrated convincingly in studies [17]. Other unsuccessful treatments regarding symptom relief or disease modification include hydroxychloroquine, adalimumab, and bisphosphonates among others [1]. Although many drugs have been examined for symptom management, there is currently no universally accepted stepwise strategy to guide practitioners in clinical care [18]. Pharmacologic measures include acetaminophen/paracetamol, NSAIDs, SNRIs, opioids, and now possibly cannabinoids. Although widely recommended as first-line treatment for OA pain, acetaminophen provided only minimal improvements in pain and function according to a review of 10 randomized controlled trials (RCTs) [19•]. While effective for OA pain, the cardiovascular, renal, and gastrointestinal risks of NSAIDs preclude use for many and have likely prompted an increase in opioid and decrease in NSAID's prescriptions between 2001 and 2012 [20]. It is estimated that about 41% of the increased cardiovascular risk in OA patients was attributable to NSAID use [21]. Patients poorly tolerant of NSAIDs are also those at most risk for opioid complications such as cognitive impairment, falls, or drug-drug interactions. Considering the limited choice of drugs to treat OA pain, we will examine the evidence for effect of opioids and cannabinoids in OA pain management.

## The debate regarding opioids and cannabinoids in OA treatment

Both opioids and cannabinoids have a history of therapeutic use spanning thousands of years. Both have analgesic properties, with cannabinoids

shown to have anti-inflammatory properties in preclinical study. Many of the problems concerning opioids pertain to cannabinoids. Both have immediate psychoactive effects, especially for medical cannabis with a higher THC content, as well as long-term effects of dependence and abuse, well documented for therapeutic opioids, and for cannabinoids when used recreationally. Cannabinoids have been touted as the answer to the opioid epidemic, but in the absence of recommendation to use opioids for OA pain, this argument is fallacious. The objective of pain management is to maintain function which raises concerns about falling when agents with psychomotor effects are used. Ability to drive is central to the independence of many in the western world, with driving impairment related to use of opioids and cannabinoids an increasing risk to safety [22]. There has been a shift in drug versus alcohol prevalence in motor vehicle decedents. Opioids and cannabinoids were identified as the second and third most prevalent substances in deceased persons in a Milwaukee county study spanning 2010 to 2016 [23]. In addition, the presence of drug positive decedents exceeded the number of alcohol-positive decedents for the first time in 2016. Drug-drug interactions, as well as the additive psychoactive effects of opioids and cannabinoids, must be addressed, especially for the elderly. Finally, both opioids and cannabinoids are a risk for dependence and addiction.

## Opioids

### The products available

The opium poppy was cultivated as early as 3400 BC in Mesopotamia, with opiates identified as naturally occurring alkaloids. Opioids is a term used to describe all compounds that target the opioid receptor and may be categorized as weak, such as codeine or tramadol, or stronger opioids such as morphine and others (Table 1) [24]. Morphine, as the first isolated opioid, is used as a reference when comparing relative potency of opioids. Codeine and tramadol are categorized as weak opioids. Codeine, close to one tenth as potent as morphine, has analgesic properties that are dependent on metabolism to morphine through the CYP2D6 pathway. Tramadol, a codeine analogue, is an atypical opioid consisting of a mixture of 2 enantiomers: a mu-opioid receptor agonist and serotonin reuptake inhibitor and a norepinephrine reuptake inhibitor. With potency similar to codeine, it may be a choice prior to use of stronger opioids.

Strong opioids include oxycodone and hydromorphone, with the latter a preferred agent in renal failure due to lower toxic metabolite accumulation [24]. Other opioids, considered second line, are more complex and potent. Fentanyl, an opioid agonist, approximately 80 times more potent than morphine, is administered via transmucosal or transdermal route due to high lipophilicity. Fentanyl is preferred in renal failure due to inactive metabolites. Methadone, a synthetic molecule unique among opioids, has high affinity for the opioid receptor, ability to inhibit serotonin and norepinephrine reuptake, and has *N*-methyl-D-aspartate receptor (NMDA) antagonist properties. Although traditionally used to treat opioid addiction, methadone is a treatment of severe neuropathic pain resistant to first-

**Table 1. Opioid products available**

| | Target | Conversion ratio in oral morphine equivalents [24, 25] * | Comments |
|---|---|---|---|
| Weak opioids | | | |
| Tramadol | - Opioid receptor agonist<br>- Serotonin reuptake inhibitor<br>- Norepinephrine reuptake inhibitor | ~1:0.15 | - Often 1st opioid used before strong opioids given its preferable safety profile [26] |
| Codeine | - Opioid receptor agonist | 1:0.15 | - Prodrug converted to morphine via CYP 2D6 at variable rates depending on polymorphism |
| Strong opioids | | | |
| Morphine | - Opioid receptor agonist | 1:1 | |
| Buprenorphine | - Opioid receptor partial agonist | 1:1 | - Longer ½ life than morphine<br>- Only available sublingual or transdermal |
| Oxycodone | - Opioid receptor agonist | 1:1.5 | |
| Tapentadol | - Opioid receptor<br>- Norepinephrine reuptake inhibitor | 1:3.3 | - Considered a 4th-line therapy for neuropathic pain [27] |
| Hydromorphone | - Opioid receptor agonist | 1:5 | - Preferred agent in renal failure given few active metabolites |
| Fentanyl | - Opioid receptor agonist | 1:80 | - Preferred agent in renal failure given no active metabolites |
| Methadone | - Opioid receptor agonist<br>- NMDA receptor antagonist<br>- Serotonin reuptake inhibitor<br>- Norepinephrine reuptake inhibitor | N/A | - Considered a 4th-line therapy for neuropathic pain<br>- Only prescribed by specifically trained professionals<br>- Extremely long half-life |

*Variable from paper to paper; information given to provide frame of reference

line opioids. Methadone has multiple drug-drug interactions, variable bioavailability, and an extremely long half-life (up to 150 h).

Atypical opioids include tramadol (described above), tapentadol, and buprenorphine. Tapentadol acts on the mu-opioid receptor and inhibits norepinephrine reuptake without affecting serotonin, an effect particularly useful for treating neuropathic pain. It is not significantly protein bound, has no active metabolites, and is not a CYP inducer or inhibitor, resulting in fewer drug-drug interactions. It also has a trend to less gastrointestinal side effects but with similar dropout rates to other opioids in clinical studies [28, 29]. Finally, buprenorphine is a semi-synthetic opioid that is a partial agonist of the mu-opioid receptor, equally as potent as morphine but with a longer duration of action. It can be administered sublingually or transdermal given its high lipophilicity and low oral bioavailability. Naloxone has been added to most sublingual formulations to reduce the risk of abuse (to prevent IM/IV effect) [24, 30].

## Evidence for effect

Opioids are the mainstay of treatment for acute pain but with questionable use for management of chronic pain in view of the risk-benefit ratio. Most studies examining the effects of opioids in chronic conditions are for a period of 8 to 12 weeks, a time frame required by drug agencies for drug approval, but with extrapolation into clinical care less reflective of real-life practice [31]. A 2014 Cochrane review of opioids for knee and hip OA included 22 trials and demonstrated a statistically significant improvement in pain relief but with failure to meet the minimal clinically significant difference. Adverse effects were significantly increased (odds ratio (OR) = 3.35), with dropout rates attributable to adverse effects calculated as an OR of 3.76. There was a trend that short-term opioid treatment ( 4 weeks) was more effective for pain reduction [31]. In a subsequent meta-analysis, Schaefert and colleagues included 22 studies with 33 treatment arms to assess effects of opioids in chronic OA pain, with the conclusion that opioids were superior to placebo in terms of efficacy but inferior regarding tolerability [18]. In a Cochrane review of tramadol in OA, with 22 RCTs included, there was moderate quality evidence that overall tramadol alone or in combination with acetaminophen had no important benefit on pain or function, but slightly more patients on tramadol achieved a clinically meaningful (≥ 20%) reduction in pain [32].

Could opioids be a better treatment option than NSAIDs in view of cardiovascular and renal risks? Similar pain relief was reported for NSAIDs and opioids for knee OA in a systematic review of 17 studies [33]. In a study among Veterans Administration patients, opioid treatment was not superior to non-opioid treatment for pain-related function or pain interference but was associated with more adverse effects [34•]. The 2012 American College of Rheumatology (ACR) guidelines recommend opioids for OA patients who have failed other treatments or are not candidates for surgery but will likely be revised considering recent study [35]. In line with current evidence, the 2019 Osteoarthritis Research Society International (OARSI) guidelines recommend *against* opioid use [36••].

## Risks related to opioids

As previously mentioned, any efficacy of opioids in OA is likely outweighed by adverse effects for both the individual and society [31, 37]. A 2019 systematic review and meta-analysis of 17 RCTs found significantly increased risks for adverse effects with immediate-release and extended-release opioids in OA patients [38••]. Overall, gastrointestinal, central nervous system, and cutaneous symptoms (rash) were more common with opioid use versus placebo [38]. Withdrawal symptoms when opioids are discontinued must be considered another potential adverse consequence [31].

Falling is associated with knee OA, and this risk will be augmented by a drug with neurocognitive or psychoactive effects [39, 40]. In parallel with an increase in opioid use from 2.7% to 3.6% over a 4-year period for 4231 participants followed from the Osteoarthritis Initiative (OAI), there was over a 20% risk of recurrent falls (opioids, $RR_{adjusted} = 1.22$, 95% CI = 1.04–1.45).

Opioids and surgery require examination. Persistent pain following total joint replacement occurs in up to 30% of patients [41]. Preoperative opioid use

in patients undergoing total joint replacement was independently associated with prolonged hospitalization, greater risk of in-hospital complications, and early revision surgery [42]. Preoperative tramadol was associated with poorer outcome as measured by the Knee Disability and Osteoarthritis Outcome Score following total knee arthroplasty in a cohort of 199 patients [43]. Similarly, opioid use was associated with less pain relief 6 months after surgery [44]. In a study of 156 patients undergoing total knee arthroplasty, preoperative Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score and Pain Catastrophizing Scale were greater for the 23% opioid users but with a mean reduction in WOMAC pain score of 27.0 vs. 33.6 points ($p = 0.008$) for opioid users vs. non-opioid users at 6 months [44]. These studies should however be interpreted with caution as there may be a risk of confounding by indication, i.e., patients with more severe pain or other health issues may have been treated by opioids prior to surgery.

Recent studies suggesting an increased mortality associated with opioid use in OA are of concern [45••]. Using a sequential propensity score-matched cohort study of 88,902 OA patients at a general practice in the UK, Zeng et al. reported a significantly increased risk of all-cause mortality over 1 year with initial prescription of tramadol compared to naproxen (hazard ratio [HR] of 1.71 [95% CI, 1.41–2.07]). Similarly, there was a higher mortality for tramadol compared with diclofenac (HR, 1.88 [95% CI, 1.51–2.35]), celecoxib (HR, 1.70 [95% CI, 1.33–2.17]), and etoricoxib (HR, 2.04 [95% CI, 1.37–3.03]) [45••]. Moreover, all-cause mortality rate was similar for tramadol and codeine suggesting a class effect. Similar to other studies of opioid use and adversity, this study may also have been subject to confounding by indication as was acknowledged by the authors. In addition, protopathic bias may have been a factor as cancer-related mortality was higher in the tramadol group.

Dependence, diversion (both illicit and within families), and abuse are a risk for patients treated with opioids. Opioids can produce hyperalgesia, leading to dose escalation and subsequent dependence. Unlike dependence, abuse and overdose are less predictable but with risks identified as higher opioid doses, long-term use (> 3 months), depression, and substance use disorder [46]. Overdose has also been associated with long-acting formulations, the time frame shortly after initiation, combination with benzodiazepines, the elderly (> 65 years of age), sleep-disordered breathing, renal or hepatic impairment, and a previous history of overdose [47]. Death from opioid overdose has increased dramatically, with over 11,000 persons dying from overdose in the USA from January 2016 to December 2018 [4•]. Furthermore, death due to opioid overdose is not confined to the young drug seeking population but also affects those with chronic pain using prescription opioids [48].

## Cannabinoids

Cannabinoids may offer a treatment option for symptom management in OA, with popular and advocacy promotion as an alternative to opioids. Apart from effect on pain and inflammation, there may be positive effects on sleep and anxiety. Concerns regarding cannabinoids include the absence of sound study, questions about long-term risks, drug-drug interactions that are unknown, and the acute psychomotor effects.

## The products available

There are two forms of cannabinoids currently available: pharmaceutical products and products derived from the *Cannabis* plant itself (Table 2). Surnamed the "plant of a thousand molecules", *C. sativa* contains a variety of molecules including delta-9 tetrahydrocannabinol ($\Delta^9$-THC) and cannabidiol (CBD), with $\Delta^9$-THC responsible for psychoactive effects. Pharmaceutical cannabinoids can be synthetic or plant-derived products with clearly defined content, studied for safety and efficacy and monitored for quality control by regulatory bodies. Nabiximols, a pharmaceutical oromucosal spray derived from the *Cannabis* plant, contains 25 mg/ml CBD and 27 mg/ml THC, with the maximal recommended dose of 12 sprays per day. Given that each spray contains 2.5 mg and 2.7 mg of CBD and THC, respectively, the maximal recommended dose of THC is approximately 30 mg daily. A second pharmaceutical preparation is nabilone, a synthetic THC analogue. Neither have been studied in OA. Herbal (medicinal) cannabis is the direct product of the *C. sativa* plant, in the form of dried flowers and leaves, or extracts of the plant that is in the form of an oil. Medicinal cannabis is not an approved medical therapy, is not regulated in terms of content, and has not yet been formally evaluated to determine optimal dosing, efficacy, and adverse effects. These herbal products are increasingly available to patients who have a medical recommendation for use, but not a formal prescription as for any other medicinal product. Furthermore, in jurisdictions where cannabis is a legal recreational product, patients are increasingly self-medicating with cannabis products.

## Evidence for effect

Even with greater access to cannabis worldwide, there is no single RCT examining herbal cannabis for efficacy or side effects in rheumatic diseases or OA in particular. Cannabinoid effects are complex, with preclinical studies showing opposing effects such as sleep promotion as well as sleep disturbance, pro and anti-anxiolytic effects, and even variable effects on inflammatory and other cell function related to the specific strain of cannabis used [52].

In a study to examine the safety of smoked cannabis for chronic pain, including musculoskeletal conditions, serious adverse effects did not differ between cannabis users and nonusers but with an increased risk of nonserious adverse events (adjusted incidence rate ratio = 1.73, 95% confidence interval = 1.41–2.13), mostly judged to be mild to moderate [53]. In the absence of RCTs of herbal cannabis in rheumatic conditions, any information about the effects of cannabinoids in rheumatology practice is based on anecdote, two small epidemiological studies, and a handful of studies of either synthetic molecules or purified cannabis extracts [51, 54–57]. There is no evidence-based information regarding recommended dosing of herbal cannabis other than patient report of amount used. Canadian rheumatologists have stated their lack of confidence in their knowledge of cannabis prompting the Canadian Rheumatology Association to publish pragmatic advice regarding use of medical cannabis with focus on safety, contraindications, methods of administration, and dosing [58, 59••].

## Risks related to cannabinoids

The risks related to cannabis should be categorized as immediate, short term, and long term. Psychoactive effects mediated mostly by THC impact cognition

**Table 2. Prescribed cannabinoid medicines available [49]**

| | Molecule | Route | Health Canada approval [50] | Available studies in rheumatic patients | Off-label use |
|---|---|---|---|---|---|
| Nabiximols (Sativex) | -Whole-plant extract of two *Cannabis sativa* strains containing THC and CBD<br>-Also contains other cannabinoids, terpenoids, and flavonoids | Oromucosal spray | 1) Adjunct for spasticity or neuropathic pain in MS<br>2) Adjunct in moderate to severe cancer related pain | Rheumatoid arthritis [51]<br>- Benefits on pain, sleep, and HRQoL<br>- Significant increase in adverse effects | - Fibromyalgia, epilepsy, and anxiety disorders<br>- Any rheumatic disease with persisting neuropathic pain prior to a trial of herbal cannabis |
| Nabilone (Cesamet) | - Synthetic THC analogue<br>*generic available | PO | 1) Severe chemotherapy-induced nausea and vomiting | Fibromyalgia (RCT)<br>- Equivalent to amitriptyline for sleep<br>- Significant increase in adverse effects | |
| Dronabinol (Marinol) | - Synthetic THC | PO | 1) Severe chemotherapy-induced nausea and vomiting<br>2) Weight loss associated with AIDS-related anorexia<br>*Removed from Canadian market by manufacturer (not for safety reasons) | Fibromyalgia retrospective study<br>- Decrease in pain, depression, and concomitant analgesics<br>- Many limitations (high dropout rate, etc.) | Not available in Canada |
| Epidiolex | - Whole-plant cannabis extract containing > 98% CBD<br>- Only oil available | PO | Not yet approved in Canada<br>USA: orphan drug designation for treatment of Lennox-Gastaut and Dravet syndrome and tuberous sclerosis complex | No | |
| Herbal cannabis | - THC and CBD among many others<br>- Fresh, dried oil, plants, and seeds | PO<br>Smoked<br>Vaporized | None | Fibromyalgia cross-sectional study<br>- Benefits on pain, stiffness, and anxiety | Trial after failure of an oral cannabinoid |

*THC* delta-9-tetrahydrocannabinol; *CBD* cannabidiol; *MS* multiple sclerosis; *AIDS* acquired-immunodeficiency syndrome; *HRQoL* health-related quality of life; *RCT* randomized controlled trial

**Table 3. Enzymatic effects of opioids and cannabinoids**

| | Clinically significant hepatic metabolism | Action as inhibitor or inducer of CYP enzymes | Examples of theoretically possible interactions via hepatic metabolism |
|---|---|---|---|
| Weak opioids [24] | | | |
| Tramadol<br>Codeine | CYP 2D6 | – | - 2D6 inhibitors will decrease their effect<br>○ E.g.. buproprion, fluoxetine, paroxetine, CBD, etc. |
| Strong opioids [24] | | | |
| Morphine | Glucuronidation<br>Demethylation | – | - Few interactions reported (avoid with other psychoactive medications) |
| Hydromorphone | Glucuronidation | | |
| Tapentadol [68] | Glucuronidation<br>Sulfidation | | |
| Oxycodone | CYP 3A4 (major)<br>CYP 2D6 (minor) | – | - Inhibitors of 3A4 can increase their effect<br>○ E.g., clarithromycin, itraconazole, voriconazole, etc. |
| Buprenorphine<br>Fentanyl | CYP 3A4 | | |
| Methadone | Variable*<br>CYP3A4 (major)<br>CYP2B6 (major)<br>CYP2D6 (minor)<br>CYP2C9 (minor) | Variable inducer of:<br>- CYP3A4 | - Given multiple active metabolites, there are variable effects resulting from enzymatic inhibition/induction<br>- Strong inducers of 3A4:<br>○ E.g., carbamazepine, phenytoin, rifampin,<br>- Strong inhibitors of 3A4 (cf. examples above)<br>-Inducers of 2B6:<br>○ E.g., carbamazepine, rifampin, efavirenz, etc.<br>-Prolongs QTc – risk of compounding effect<br>○E.g., fluoroquinolones, citalopram, domperidone, etc. |
| Cannabinoids | | | |
| CBD [69] | Predominantly phase I enzyme metabolism | Inhibitors of:<br>- CYP3A4/3A5<br>- CYP 2C19 and 2D6<br>If smoked:<br>- Inducers of CYP 1A2 | -Increased effects/side effects of medications metabolized by these enzymes (particularly C3A)<br>○E.g., prednisone and hydrocortisone, amitriptyline, gabapentin, pregabalin, etc.<br>-May decrease effect of prodrugs like tramadol and codeine |
| THC [50] | CYP 2C9<br>CYP 2C19<br>CYP 3A4 | | -Same effects as CBD<br>-Inhibitors of 2C9 and 3A4 can increase drug levels<br>-Inducers of 3A4 can decrease drug levels |

and alertness. Even some products marketed as CBD have been shown to contain variable amounts of THC, with warnings issued by the Federal Drug Agency (FDA) [60]. Although never examined in patients, young healthy recreational cannabis users had impaired psychomotor function after acute

cannabis use when tested for driving competence [22]. This effect is likely augmented by illness, age, comorbid disease, and other medications. Therefore, risks of falls are a potential risk for persons with OA using medical cannabis. Acute cardiovascular events are associated with cannabis use [61]. Richards and colleagues evaluated 85 publications involving over half a million subjects regarding cannabis and cardiovascular risks and concluded that all but 5 out of 33 Level 1–111 publications highlighted a risk of acute coronary events and chronic cardiovascular disease associated with cannabis use [62•]. Extrapolation of the risks of recreational cannabis to the medical population is acknowledged to be inaccurate but in the absence of such studies in patient populations must at this time be used to give some message and guidance.

Cannabis is an addictive substance [63]. The long-term risks of addiction may seem less important in an older population with OA but must still be kept in mind pending further study. Although extrapolation from recreational use is not ideal, information about addiction in recreational users must be used to inform medical use until better information is available.

## Current debates in the field of medical cannabis

Preclinical studies of cannabis show promise for analgesia but cannot be accepted as proof of effect in the clinical setting. Good science is slowly emerging and must be strongly disseminated, although there is currently a risk of dilution of the scientific message by the mass of poor publications. For example, different strains of cannabis with equivalent concentrations of CBD and THC can have different effects on cell function which could easily have an impact on clinical efficacy [52]. The greatly promoted outstanding effect of CBD for severe uncontrolled epilepsy may be due to drug-drug interaction with the drug clobazam, rather than a unique effect of CBD, a finding that could put patients at risk if they were to change their anti-seizure medication [64, 65]. The original report that opioid deaths were reduced in US states with legal access to cannabis is now challenged as opioid overdose mortality has increased by 23% when the original analysis from 1999 to 2010 was extended to 2017 [66, 67]. Finally, there remains a critical dearth of any study of cannabis in patients with OA.

## Main drug interactions of opioids and cannabinoids

The clinical relevance of drug-drug interactions of both opioids and cannabinoids are likely more important for the additive pharmacodynamic effects of agents with tranquilizing or psychoactive effects, with perhaps less true clinical impact from effect on metabolic pathways. Although there is considerable knowledge of drug metabolism effects for opioids, less is known about cannabinoid drug interaction. Most opioids and cannabinoids are metabolized by liver cytochrome P450 enzymes and have potential for drug-drug interactions, although generally considered rare for morphine (Table 3) [24, 70]. With considerable heterogeneity in the CYP2D6 enzymatic activity in the population, some patients will be more susceptible to both analgesic and adverse effects of opioids, as well as drug-drug interactions. For example, inhibitors of 2D6 such as bupropion and fluoxetine will decrease levels of a prodrug such as codeine but may increase levels of an active drug such as oxycodone [24]. Fentanyl, methadone, and buprenorphine are metabolized by CYP 3A4, an enzyme that is inhibited by drugs such as venlafaxine [24, 30]. Methadone has the highest risk for drug-drug interactions as multiple CYP

P450 enzymes are involved in metabolism. In addition, methadone has the potential to increase QTc interval leading to torsade de pointes, with increased risks when coadministered with some antibiotics, antiepileptics, or antipsychotics [24]. Methadone can also induce enzymes involved in its own metabolism subsequently altering expected drug levels. All opioids should be used with caution in patients using monoamine oxidase inhibitors due to the risk of serotonin syndrome. Most concern about drug interactions with cannabinoids is the additive pharmacodynamic effects, especially when combined with drugs with psychoactive effects. Although the metabolism of cannabinoids, particularly THC and CBD, is known, the specific drug-drug interactions are less well understood, and most information is theoretical [70]. Both THC and CBD inhibit CYP2D6 which could result in increased levels of some antidepressants, beta-blockers, antiepileptics, and some antipsychotics. For prodrugs, such as tramadol, that require metabolism to the active drug, administration of an enzyme inhibitor may lead to poor efficacy due to reduced amount of the active drug.

## A practical approach to treating OA pain

Management of OA pain should be patient-centered with attention to functional status, comorbid disease, the severity of pain, and expected outcome goals. Non-pharmacological measures must always be instituted with education, health-related physical activity, and good lifestyle habits central to clinical care. Pharmacologic measures may be introduced in a stepwise way (as discussed by other authors), before any consideration of use of opioids or cannabinoids. Although the 2012 ACR guidelines recommended opioid use in selected cases, newer evidence speaks against this use due to questionable clinical benefit and serious concerns about risks, including the current international opioid crisis [35]. From the pragmatic and clinical viewpoint, opioids may be a treatment option for some patients with OA that experience unacceptable pain, poorly managed by other strategies and in whom surgery in not an option. The 2017 Canadian guidelines for opioid use in non-cancer chronic pain recommend starting at the lowest dose possible and titrating upward slowly, with total daily dose of morphine equivalent less than 90 mg and preferably below 50 mg. Prescriptions should be provided by the primary treating physician only for a period of a month and with a trial limited to 3–6 months. If ineffective, opioids should be discontinued [71]. There are no guidelines regarding cannabinoid use in OA but, like opioids, should only be tried when other treatments have failed. The 2019 Canadian Rheumatology Association position statement concluded that there was insufficient evidence about the benefits of cannabinoids in a variety of rheumatic conditions, including OA, but there was high risk of harm [59••]. Extrapolating from cannabinoid use in other chronic pain states, it is possible that they may provide some symptom relief in some patients. Physicians must ensure that patients are well-informed about the evidence for benefit and risks, and like opioids, initiation of treatment must be understood to be a treatment trial, which must be discontinued if there is lack of effect or adverse effects.

## Conclusion

In summary, although OA is one of the most prevalent diseases, there are still limited therapeutic options with proven efficacy and an acceptable safety

profile. Opioids have been used as last-line therapy for years, but there is growing evidence for less favorable effects and concerns for adverse effects and abuse. Cannabinoids have been touted as the solution to the opioid crisis in the media; however, there remains limited quality data regarding use and safety in OA patients. It is important for physicians to be aware of these controversies to facilitate pragmatic discussion with patients concerning risks and benefits of both cannabinoids and opioids in OA. High-quality RCTs are required in order to better evaluate the efficacy and safety of cannabinoids in patients with OA.

## Compliance with ethical standards

**Conflict of interest**
The authors declare that they have no conflicts of interest.

**Human and animal rights and informed consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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## Publisher's Note