Review

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Review

Individualized Management of Osteoarthritis: The Role of Pharmacogenomics to Optimize Pain Therapy

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Abstract: Osteoarthritis (OA) is a multifactorial, degenerative joint disease that significantly impairs mobility and quality of life, especially among older adults. The growing aging population and increasing obesity rates are expected to increase the incidence and prevalence of OA. In the absence of Disease Modifying Antirheumatic Drugs (DMARs) for OA, current treatment strategies largely focus on symptom relief rather than disease modification and often fail to account for the substantial inter-individual variability in drug response. Pharmacogenomics (PGx), the study of how genetic variation influences drug response, offers a promising approach to personalize OA therapy. This review explores the clinical and pharmacogenomic considerations of commonly used OA medications - acetaminophen, NSAIDs, duloxetine, and tramadol - focusing on gene-drug interactions that influence efficacy, safety, and metabolism. Evidence-based recommendations from the Clinical Pharmacogenetics Implementation Consortium guidelines are discussed where applicable to highlight actionable genetic variants such as *CYP2D6*, *CYP2C9*, *CYP2E1*, and *UGT1A6*. While PGx data is not currently embedded in OA clinical treatment guidelines, its integration into clinical practice may enhance therapeutic outcomes and minimize adverse effects. This review underscores the potential of PGx as a clinical tool in OA pain management, paving the way toward truly personalized medicine.

Keywords: osteoarthritis; pain; pharmacogenomics; NSAIDs; acetaminophen; analgesics; duloxetine

1. Background

Osteoarthritis (OA) is a heterogeneous degenerative joint disorder characterized by synovial inflammation, cartilage degeneration, joint and ligament damage, and osteophyte formation.[1] OA is the most common arthritic condition, affecting more than 60 million Americans.[2,3] OA commonly affects the weight-bearing joints, mainly the hips, knees, hands, lower back, and neck. With the growing of the aging population, the prevalence of OA is expected to significantly increase over time. The prevalence of OA disproportionately affects women and dramatically increases after menopause.[4] Immune-mediated and metabolic-triggered inflammation appears to be a key component of the degeneration of bone and cartilage in OA.[3] Activity limitations and social isolation as a result of OA can lead to an increased risk of depression and reduced productivity and quality of life.[2]

Developing OA is a complex and multifactorial process influenced by both genetic and environmental factors. Thus far, 77 high-confidence effector genes have been identified through a large meta-analysis across over 800,000 patients. [5] These findings underscore the polygenic nature of OA and point to specific molecular pathways involved in cartilage degradation, inflammation, and joint remodeling.[6] Continued research into these genetic targets holds promise for the development of precision medicine approaches and disease-modifying therapies for OA.

A comprehensive, multidisciplinary approach to OA management should include lifestyle modifications such as weight reduction, regular physical activity, smoking cessation, and

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engagement in occupational or physical therapy.[7,8] Despite these strategies, there are currently no disease-modifying drugs or curative treatments for OA; the only treatments that exist are to target pain as a result of OA and improve function.[9] The 2019 guidelines from the American College of Rheumatology (ACR) and Arthritis Foundation for the management of OA strongly recommend oral non-steroidal anti-inflammatory drugs (NSAIDs) for hand, knee, and hip OA, topical NSAIDs for knee OA, and intra-articular steroids for knee and hip OA. However, acetaminophen, duloxetine, and tramadol are conditionally recommended for hand, knee, and hip OA. [7]

Inter-individual variability in response to OA treatments is well-documented and influenced by a range of factors, including age, comorbidities, lifestyle, and notably, genetics.[10,11] Genetic differences can significantly impact treatment outcomes, helping to distinguish between normal and poor responders. Pharmacogenomics (PGx), the study of how genetic variations influence an individual's response to medications, is an emerging field within precision medicine that offers a personalized approach to therapy. By analyzing variations in genes involved in pharmacokinetics and pharmacodynamics, PGx can help predict how patients metabolize and respond to specific drugs.[12] While current pharmacogenomic data is not directly linked to the causes of OA, it may help guide current treatments based on a patient's specific drug-metabolizing enzymes encoding genes. This ultimately allows tailored medication decisions that can potentially reduce adverse drug reactions (ADRs) and enhance treatment efficacy. This review aims to further explore the intersection of OA pain management and pharmacogenomics, with a focus on improving individualized drug selection to optimize clinical outcomes.

2. Pharmacological Management of OA

2.1. Acetaminophen

2.1.1. Pharmacotherapy

Acetaminophen (APAP) is an over-the-counter medication and a widely used analgesic and antipyretic for managing mild to moderate pain and or fever. According to the ACR, APAP is conditionally recommended for hip, knee, and hand OA patients. The effect sizes for acetaminophen are relatively small, suggesting that those treated with APAP may not experience the intended clinical benefits. Additionally, the use of APAP may be ineffective as a monotherapy, which supports the conditional recommendation of using APAP in OA patients.[7] Nevertheless, its favorable safety profile makes it a reasonable first step, especially for patients with limited pharmacological options or contraindications to using other treatment modalities. Collectively, APAP may be appropriate for short-term and episodic use for OA-related pain.

Acetaminophen overdose is a significant and serious health concern in the United States. It is estimated that there are up to 80,000 overdoses annually, some resulting in death from liver failure.[13] The US Food and Drug Administration has issued warnings regarding potential liver injury when using more than four grams of APAP daily and has additionally proposed an administrative order in June of 2024 that would require drug manufacturers to add a warning of the risk of rare but serious skin reactions. [14]

2.1.2. Mechanism of Action

The mechanism of action of acetaminophen is not fully understood. However, different pathways have been proposed that collectively may explain the analgesic effects of acetaminophen. Some evidence suggests that APAP inhibits the activity of COX-1 and COX-2 enzymes, which are involved in the production of prostaglandins.[15] Physiologically, prostaglandins are produced in response to tissue injury and increase pain signaling. However, acetaminophen is a weaker inhibitor of COX enzymes than traditional nonsteroidal anti-inflammatory drugs (NSAIDs), which could explain the lack of anti-inflammatory effects of APAP compared with NSAIDs.[16] Studies also suggest that acetaminophen may selectively block a distinct isoform of the COX enzyme, unlike

 doi:10.20944/preprints202505.0436.v1

COX-1 and COX-2. This enzyme has been referred to as *COX-3*.[16,17] While it was previously hypothesized that the majority of APAP analgesic effects were from COX inhibition, however more data has revealed that the main analgesic pathway is via conversion of APAP to active metabolite *N*-acylphenolamine (AM404) which acts on both cannabinoid 1 (CB1) receptor and transient receptor potential vanilloid 1 (TRPV1). The TRPV1 receptor is located on the dorsal horn of the spine, which is a well-known location within the pain pathway and is involved in modulating nociceptive pain signals.[15]

The antipyretic actions of acetaminophen are likely attributed to direct action on heat-regulating centers in the brain, resulting in peripheral vasodilation, sweating, and loss of body heat.[18] Acetaminophen metabolites may also activate CB receptors, modulating pain perception. Further, it is proposed that acetaminophen can activate the descending serotonergic pathways, creating an analgesic effect.[15] Additionally, it was proposed that the endogenous opioid pathway is activated by APAP, leading to analgesic effects.[19]

2.1.3. Clinical Pharmacology

It is well established that APAP has both analgesic and antipyretic abilities. Doses of 3,000 mg once or 1,000 mg every six hours for up to 48 hours have not shown a significant impact on platelet aggregation regardless of history of hemophilia.[20] APAP does not exhibit anti-inflammatory effects. APAP is not highly protein-bound and has a half-life of 1.5 to 2.5 hours.

UDP Glucuronosyltransferase Family 1 Member A (UGT1A) enzymes are involved in the initial steps of APAP metabolism.[21] Glucuronidation is the main pathway of acetaminophen metabolism, followed by sulfation, and a minor contribution from the oxidation route by the cytochrome P450 (CYP450) enzymes. Oxidative metabolism by CYP2E1 yields a reactive metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI), further detoxified by the glutathione pathway, converting NAPQI to cysteine and mercapturic acid conjugates at normal dosages less than 4 grams daily. Beyond a therapeutic dose, APAP is mostly converted to pharmacologically inactive APAP-glucuronide, 52–57%, and APAP-sulfate, 30–44%, with a minor fraction being oxidized to a reactive metabolite NAPQI (5–10%). Less than 5% of APAP is excreted unchanged. NAPQI is highly reactive and is primarily responsible for acetaminophen-induced hepatotoxicity in the event of APAP overdose. The formation of NAPQI is the primary result of CYP2E1, CYP1A2, and CYP3A4 metabolism.[22]

2.1.4. Pharmacogenomics

While APAP undergoes extensive metabolism through CYP450 enzymes, there remains a lack of guidance regarding dosing strategies based on different CYP2E1 genetic variants. CYP2E1 plays a key role in forming NAPQI, the metabolite primarily responsible for inducing liver injury, which is cleared via glucuronidation in phase two metabolism and is then mainly excreted through the kidneys.[22] Patients who have impaired glucuronidation may be at an increased risk for developing APAP toxicity. Conditions such as Gilbert's syndrome can impact this pathway, resulting in a higher risk for hepatic injury. While there is limited data on the impact of UGT1A gene variants on APAP metabolism, one small study showed less APAP clearance for patients with *UGT1A6*2/*2* variant when compared to *UGT1A6*1/*1*.[23] Recent data has also emerged showing significantly higher drug exposure for patients who have *UGT1A6*2* and *UGT1A6*4* variants when taking a single dose of APAP.[21] These findings collectively suggest that reduced UGT1A6 activity could contribute to the potential risk of APAP-induced liver toxicity.

Patients with normal or increased glucuronidation activity may experience a lower incidence and risk of liver injury from APAP. Patients of Asian descent may have a clinically significant lower incidence of liver failure when compared to other ethnicities in the setting of APAP overdose. One study found that 33% of patients of Asian descent displayed increased glucuronidation when compared to 20% of patients of Caucasian descent.[24] Additionally, retrospective case reviews of APAP overdose showed supporting results that Asian patients are less likely to have hepatoxicity as

 doi:10.20944/preprints202505.0436.v1

a complication.[25] This racial difference in APAP-induced liver injury risk could be partly attributed to the differential allele frequencies of UGT1A6.

Alterations in CYP2E1 enzymatic activity, particularly due to alcohol consumption, can significantly impact APAP metabolism. Chronic alcohol intake is known to upregulate CYP2E1 expression, leading to enhanced conversion of APAP to its hepatotoxic metabolite, NAPQI. While it is not defined clinically, it is reasonable to consider the possibility that increased metabolism of APAP to the toxic metabolite could result in an increased risk of liver damage, especially if the patient has a decreased ability to eliminate NAPQI via glucuronidation. Additionally, chronic alcohol abuse or underlying hepatic cirrhosis can alter the metabolism of APAP and could increase the risk of toxicity.[26]

2.1.5. Clinical Implications

APAP can be a useful agent in a multimodal pain approach for patients with OA. Special precautions regarding reduced hepatic function should be considered to limit the total daily dose to 2,000 mg. Additionally, data have been shown to implicate APAP intoxication with the risk of acute kidney injury (AKI).[27] After adjustment for age, sex, and comorbidities, patients with APAP intoxication were associated with an increased risk of AKI compared with those without APAP intoxication (adjusted HR [aHR]=2.41, 95% CI=1.31–4.44).[28] A systematic review and meta-analysis found that patients without a history of renal impairment using chronic APAP had a 23% higher risk of developing renal impairment compared to no use of APAP and proposed that acute tubular necrosis is associated with APAP use as the potential cause of impairment.[29] Per the package insert for patients with severe renal impairment, defined as a creatinine clearance ≤ 30 mL/min, a lower total daily dose of APAP and increased dosing interval should be utilized. As many patients with OA are older adults, the potential for renal and hepatic dysfunction is increased when compared to younger patient populations.

It is important to consider potential drug-drug interactions when choosing pharmacotherapy for OA. Many older adults chronically take multiple medications, including warfarin, which can have the potential to interact with APAP. Chronic use of APAP at 4,000 mg daily in conjunction with the use of anticoagulants has been shown to increase the international normalized ratio (INR) in some patients.[30] A small double-blind placebo-controlled trial was conducted to determine the impact of APAP on INR.[30] Compared to the control group, patients taking 2 g/day of APAP for two weeks showed a statistically significant increase in INR of 0.7 (95% CI 0.27-1.2, p=0.01). For the group receiving 4 g/day, mean increase in INR at week 1, 2 and 3 were reported as follows 0.5 (95% CI 0.08–0.9, p=0.04), 0.6 (95% CI 0.21–1, p=0.01), and 1.0 (95% CI 0.48–1.5, p=0.01), respectively. Close monitoring of INR for patients on warfarin should be conducted for patients who chronically use APAP.

Potential medications or other substances that could impact the CYP2E1 enzyme could also alter APAP metabolism and potentially increase the risk of hepatic injury. CYP2E1 is induced by several substances, including acetone, alcohol consumption, and isoniazid.[31] When induced, CYP2E1 can rapidly convert APAP to the toxic metabolite NAPQI.[23] Patients who are rapid metabolizers or ultra-rapid metabolizers of CYP2E1 (i.e., higher transcriptional activity) may be at higher risk for APAP toxicity or drug-induced liver injury. Nonetheless, there is limited data to substantiate the effect of CY2E1 phenotype on drug-induced liver injury. Given these metabolic complexities, consideration of both environmental factors and individual genetic makeup, particularly polymorphisms in *CYP2E1* and *UGT1A* genes, may be valuable in identifying patients at higher risk for APAP-induced hepatotoxicity.

One of the primary risks associated with high-dose acetaminophen (APAP) use is hepatotoxicity. In cases of suspected acute toxicity from a single ingestion, serum levels should be measured and monitored. A level greater than 150 mcg/mL within four hours after ingestion is considered toxic regardless of symptoms, based on the Rumack–Matthew nomogram. Liver function tests (LFTs) and coagulation panel (PT/INR) should also be monitored. Notably severe toxicity can elevate LFTs within 8 to 12 hours of ingestion. [32] Routine monitoring of LFTs for chronic use of APAP is not

 doi:10.20944/preprints202505.0436.v1

listed in the package insert, however, it may be prudent to monitor hepatic parameters in individuals with pre-existing liver disease or those concurrently taking other hepatotoxic medications.

2.2. Non-Steroidal Anti-Inflammatory Drugs

2.2.1. Pharmacotherapy

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to manage various conditions, ranging from mild pain such as headaches to major conditions such as ductus arteriosus repair. Also, the use of NSAIDs is ubiquitous in rheumatology due to their analgesic effectiveness across different disease states, including rheumatoid arthritis and osteoarthritis. Unlike many other analgesic drug classes, NSAIDs are widely available without a prescription in the United States, which may make them safe for some patients to use without medical supervision. Nonetheless, the use of NSAIDs is also associated with increased risk for ADRs, including bleeding, increased blood pressure, fluid retention, and cardiovascular events.[33]

Osteoarthritis is associated with increased morbidity and disability and episodic pain flares which could be crippling for some patients. Reducing and managing pain is a primary treatment goal for patients with osteoarthritis. There is a strong body of evidence to support the use of oral NSAIDs to manage pain among patients with polyarticular osteoarthritis and the use of topical NSAIDs for patients with knee osteoarthritis. According to the most recent ACR guidelines, NSAIDs are strongly recommended for the OA of the knee, hip, and hand due to their proven efficacy in reducing pain and improving function.[7] Both oral and topical NSAIDs are endorsed, with topical formulations preferred for knee and hand OA, particularly in older adults or those at higher risk for gastrointestinal or cardiovascular side effects. The ACR emphasizes using the lowest effective dose for the shortest possible duration to minimize ADRs.

2.2.2. Mechanism of Action

The anti-inflammatory effects of NSAIDs are primarily mediated by decreasing the production of prostaglandins through inhibiting the cyclooxygenase enzyme (COX). Various NSAIDs may have additional mechanisms of action, including inhibiting chemotaxis, downregulating IL-1 production, decreasing the production of free radicals and superoxide, and interfering with calcium-mediated intracellular events.[34] Multiple isoforms of COX enzymes represent multiple targets for therapeutic purposes. The COX-2 enzyme is mainly expressed during the inflammatory response to tissue injury, while COX-1 is constitutively expressed to maintain normal physiological functions.[35] Selectivity for COX-1 versus COX-2 is variable and incomplete for different NSAIDs. However, drugs with high COX-2 selectivity do not affect platelet functions at their usual doses and are associated with reduced risk for gastrointestinal bleeding compared with non-COX-selective drugs.[36]

2.2.3. Clinical Pharmacology

NSAIDs, as a pharmacologic class, exhibit substantial variability in their half-lives, metabolic pathways, and selectivity for COX enzymes (see Table 1). These differences have important clinical implications for drug selection, dosing schedules, and safety monitoring. Most NSAIDs are metabolized hepatically via cytochrome P450 (CYP) enzymes, primarily CYP2C9, with additional contributions from CYP3A4 and CYP1A2, and are subsequently eliminated as metabolites through renal excretion. Common NSAIDs that undergo significant CYP2C9 metabolism include ibuprofen, celecoxib, meloxicam, piroxicam, diclofenac, and indomethacin. Given the central role of CYP2C9 in the biotransformation of many NSAIDs, pharmacogenetic guidance is available to inform dosing in individuals with reduced metabolic capacity, thereby minimizing the risk of ADRs and enhancing therapeutic precision.[37]

The elimination half-lives of NSAIDs also differ, which dictate how frequently they must be administered. The majority of NSAIDs require multiple daily doses to maintain therapeutic plasma levels. However, agents with longer half-lives, such as meloxicam, piroxicam, and nabumetone, can

 doi:10.20944/preprints202505.0436.v1

be dosed once daily, which may improve adherence in patients requiring chronic anti-inflammatory therapy (see Table 1).[38] The elimination of NSAIDs and their metabolites is primarily by the kidneys; therefore, it is important to consider renal function when initiating or adjusting therapy. Moreover, NSAIDs can impair renal perfusion by inhibiting prostaglandin synthesis, particularly in patients who are volume-depleted, elderly, or have preexisting renal impairment, thus increasing the risk of acute kidney injury.[39]

Table 1. NSAID Clinical Pharmacology.

NSAID	COX Enzyme Selectivity	Half-Life (Hours)	Recommended Anti-Inflammatory Dosing	Major Metabolizing Enzymes	Minor Metabolizing Enzymes	Considerations
Ibuprofen	COX-1 & COX-2	2-4	600-800mg QID	CYP2C9	CYP2C19 and CYP2C8	Concomitant administration with aspirin antagonizes the antiplatelet effects of aspirin
Celecoxib	COX-2	11-13	100-200mg BID	CYP2C9	CYP3A4	
Flurbiprofen	COX-1 > COX-2	5-6	300mg TID	CYP2C9	Enterohepatic circulation	
Ketoprofen	COX-1 > COX-2	2-4	75mg TID	Hydroxylation & glucuronidation		
Meloxicam	COX-2>> COX1	15-20	7.5–15mg QD	CYP2C9	CYP3A	
Piroxicam	COX-1 & COX-2	30-86	20mg QD	CYP2C9		
Diclofenac	COX-2>> COX1	2	50-75mg BID	CYP2C9 & UGT2B7	CYP2C8, CYP3A4	
Naproxen	COX-1 & COX-2	12-17	375-750mg BID	UGT2B7	CYP1A2, CYP2C8, CYP2C9	
Nabumetone	COX-2 > COX-1	19-36	1-2gm QD	CYP1A2 & CYP2C9	Glucuronidation	Prodrug with active metabolite
Indomethacin	COX-1 > COX-2	4-5	25-50mg TID	CYP2C9		
Etodolac	COX-2>> COX1	5-8	300-500mg TID	Hydroxylation & glucuronidation		
Sulindac	COX-2 > COX-1	8-16	150-200 mg BID		Enterohepatic circulation, CYP1A1	Prodrug with active metabolite
Ketorolac	COX-1	2-9	10mg QID	Hydroxylation & glucuronidation, OAT1/3		Oral formulation not for initial therapy, max 5 days of therapy

 doi:10.20944/preprints202505.0436.v1

2.2.4. Pharmacogenomics

A major metabolic pathway for NSAIDs involves CYP2C9. This pathway has the most well-established pharmacogenetic recommendations. Individuals with CYP2C9 *2/*3 or *3/*3 are classified as poor metabolizers (PM), while those with *1/*2, *1/*3, or *2/*2 are considered intermediate metabolizers (IM). Both PM and IM may have increased plasma concentrations of the NSAID, resulting in increased risk for ADRs. For NSAIDs predominantly metabolized by CYP2C9, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines recommend using the lowest effective dose and titrating cautiously in patients who are CYP2C9 IMs or PMs.[37]

For NSAIDs with short to long half-lives metabolized by CYP2C9 (ibuprofen, celecoxib, flurbiprofen), CPIC recommends reducing the starting dose to 25-50% of the lowest starting dose and 25-50% of the normal maximum dose in addition to close monitoring for adverse effects in CYP2C9 PM.[37] Reduced CYP2C9 enzymatic activity, especially among the PM phenotypes, may extend the half-life of these NSAIDs, and therefore, longer titration should be considered when increasing doses. Individuals with CYP2C9 IM status, no dose adjustments are recommended unless the CYP2C9 activity score (AS) is less than 1.[37] For those patients, CPIC recommends using the lowest starting dose and titrating slowly, especially when other risk factors for adverse effects are present (see Table 2). Most guideline-directed dosage adjustments for variations in drug-metabolizing enzyme activities are related to safety outcomes rather than efficacy. Nevertheless, genetic variants of the COX-2 gene have been investigated to compare the pharmacodynamics of oral NSAIDs. Two alleles were identified, rs5275 and rs689466, and determined to affect the pharmacodynamic response to celecoxib.[40] These two variants were the most common at 46% and 18%, respectively. While no difference in drug exposure was observed, the GG genotype of the rs689466 variant had a significantly lower area under the effect curve, which may indicate a varying level of COX-2 inhibition for those specific patients.[40] While this data may demonstrate a relationship between COX-2 gene variants and NSAID response, more data is needed to determine the relationship between the genetic variability in drug metabolism and drug selection for efficacy outcomes.

Table 2: CPIC Dosing Recommendations for Ibuprofen and Celecoxib based on CYP2C9 Phenotype (Theken et. al, 2020).

CYP2C9 Phenotype	PK Implication	Therapeutic Recommendation	Classification of Recommendation	Other Considerations
Normal metabolizer	Normal metabolism	Initiate with the recommended starting dose per package label	Strong	
Intermediate metabolizer (AS 1.5)	Mildly reduced metabolism	Initiate with the recommended starting dose per package label	Moderate	Higher than normal risk of ADRs, particularly if other factors affecting the clearance of NSAIDs are present. Individuals carrying the CYP2C9*2 allele have an 80% chance of also having the CYP2C8*3 allele, also involved in ibuprofen metabolism.
Intermediate metabolizer (AS 1)	Moderately reduced metabolism	Initiate therapy with the lowest recommended starting dose	Moderate	Higher than normal risk of ADRs, particularly if other factors affecting the clearance of NSAIDs are present.

 doi:10.20944/preprints202505.0436.v1

				Individuals carrying the CYP2C9*2 allele have an 80% chance of also having the CYP2C8*3 allele, also involved in ibuprofen metabolism.
Poor metabolizer	Significantly reduced metabolism	Initiate therapy at 25-50% of the lowest recommended starting dose. Titrate up to 25-50% of the maximum dose based on clinical effect	Moderate	May consider alternative therapy that is not metabolized by CYP2C9, such as ketorolac or naproxen.

2.2.5. Clinical Implications

NSAIDs have robust data for efficacy for pain management, both acute and long-term, for OA.[10] Although NSAIDs have proven effective for the management of various pain conditions, it is important to consider the risks associated with their use. There is a well-defined increased risk of GI bleeds with NSAID use, particularly those that are COX-1 selective. COX-2 selective NSAIDs, while having a lower GI bleed risk, do possess potential cardiovascular impacts.[41] There is a large body of evidence that links COX-2 selective NSAIDs with the potential of cardiovascular events such as myocardial infarction, stroke, and heart failure.[42,43] Patients with a history of cardiovascular disease should avoid the use of COX-2 selective NSAIDs and NSAIDs altogether if possible.

Topical NSAIDs such as diclofenac are an alternative NSAID option with less systemic absorption than traditional oral NSAIDs. Diclofenac is available as a prescription medication and over the counter. The ACR recommends the use of topical NSAIDs for knee OA and conditionally for hand OA. Topical NSAIDs have shown no increased risk of GI bleeding when compared to placebo.[44] A meta-analysis of trials comparing oral to topical NSAIDs found no significant difference in mean efficacy for pain control in patients with OA.[45] GI adverse reactions were significantly lower in the topical NSAID groups than in the oral NSAID groups (OR, 0.30; 95% CI, 0.16, 0.56; P = .0001). Whereas the incidence of skin reactions was over five times greater in the topical NSAID than the oral group (OR, 5.22; 95% CI 2.01, 13.56; P = .0007).[45]

Caution should be employed when utilizing NSAIDs in conjunction with other agents that increase bleeding risk, such as anticoagulant medications. GI protection in the form of acid-reducing medications, such as proton pump inhibitors or histamine receptor 2 antagonists, may be utilized if a patient necessitates therapy with an oral NSAID or while on anticoagulation medications. The use of NSAIDs in older adults is also of concern due to the safety profile and increased risk of ADRs, particularly GI bleeding.[46] Careful consideration should be made before prescribing or recommending NSAIDs for the treatment of OA in older adults >65 years old, particularly if they are taking anticoagulants, have a history of GI bleeds, or any other conditions putting them at higher bleed risk.[41]

An increase in blood pressure has also been linked to chronic NSAID use, although the degree varies depending on the NSAID used.[47]–[50] Data has shown an increase in mean arterial pressure of up to 3 mmHg when using indomethacin, and up to 1 mmHg when using ibuprofen. [47] Another meta-analysis established an overall increase in mean blood pressure of 5.0 mmHg (95% CI, 1.2 to 8.7 mmHg) for all NSAIDs pooled.[43] Patients with underlying cardiac disease or hypertension are not ideal candidates for the use of NSAIDs to treat OA pain. If deemed clinically necessary, their use should be sparing at the lowest effective dose with the least systemic exposure possible.

Additionally, NSAIDs have the potential to impact renal function. Older adults with underlying hepatic dysfunction, preexisting nephrotic syndrome, poor baseline renal function, or proteinuria are

 doi:10.20944/preprints202505.0436.v1

at an elevated risk for renal function decline in the setting of NSAID use. [51] Exercising caution is important in patients with such risk factors when initiating NSAIDs in older adults.

2.3. Duloxetine

2.3.1. Pharmacotherapy

Patients with OA can have a high disease burden due to limited mobility and reduced quality of life. Taken together, depression and depressive symptoms are well-documented in patients with an OA diagnosis. Indeed, the prevalence of depression diagnosis among patients with OA is approximately 20%.[52] To this end, in evaluating patients with OA, screening for depression could be warranted. Concurrently, centrally acting agents, such as SNRI and SSRI, widely prescribed for depression, have been used in the management of chronic pain. However, only duloxetine, which has shown adequate evidence for its use in OA.[53] Duloxetine is a potent serotonin and norepinephrine reuptake inhibitor that modulates pain in the central nervous system.[54] It is assumed that duloxetine inhibits pain activity via serotonergic and noradrenergic neurons in the descending spinal pathway. According to the ACR guidelines, duloxetine is conditionally recommended for knee, hip, and/or hand OA patients.[7] Nevertheless, exercising caution should be in place when prescribing duloxetine to patients with underlying cardiovascular and gastrointestinal comorbidities. Combination therapy of duloxetine and NSAID in patients with OA, though, could benefit patients to achieve greater pain control, monitoring, and counseling the patients for increased risk of bleeding is warranted.

2.3.2. Mechanism of Action

Duloxetine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake.[54] Increasing the concentration of serotonin and norepinephrine in the dorsal horn of the spinal cord increases descending inhibition of pain through activation of different 5-HT subtypes, α_1-adrenergic, and α_2-adrenergic receptors.[54,55] Duloxetine's hypertensive effect is related to its intended pharmacological effect. Increased availability of norepinephrine leads to activation of adrenergic receptors on the vascular endothelium. Since the action of α_1 receptors predominates in the vasculature system, vasoconstriction is mediated by calcium release from the sarcoplasmic reticulum to facilitate smooth muscle contraction.[54]

2.3.3. Clinical Pharmacology

Duloxetine is extensively metabolized via CYP450 enzymes, primarily CYP1A2 and CYP2D6.[56] The hydroxylated metabolite is further metabolized via glucuronidation. About 70% of duloxetine is excreted in the urine mainly as conjugated metabolites.[57] Another 20% is present in the feces as the parent drug and inactive metabolites, including 4-hydroxy duloxetine glucuronide (M6), 6-hydroxy-5-methoxy duloxetine sulfate (M10), and 4,6-dihydroxy 6 duloxetine metabolite. Duloxetine has an elimination half-life of about 12 hours (range 8 hours to 17 hours), and its pharmacokinetics are dose-proportional over the therapeutic range.[57] Steady-state plasma concentrations are typically achieved after 3 days of dosing.[56]

2.3.4. Pharmacogenomics

Several genes of interest are involved in the pharmacokinetics and pharmacodynamics of duloxetine, which include CYP2D6, HTR2A, and SLC6A4. CYP2D6 is one of the metabolizing enzymes of duloxetine, while HTR2A is a gene that encodes for 5HT2A receptors, and SLC6A4 encodes for the protein that transports serotonin back into the receptor.[58] There is currently no data that suggests alterations in either HTR2A or SLC6A4 genes warrant dose adjustments or a change in duloxetine therapy. The 2023 CPIC guideline currently concludes that the existing data do not demonstrate a clinically meaningful impact of CYP2D6 genotype on duloxetine therapy or

 doi:10.20944/preprints202505.0436.v1

metabolism when used for the treatment of depression.[59] Several studies have found that duloxetine serum concentration is increased more than two-fold in CYP2D6 PM, defined as **3/*4, *4/*4, *5/*5, *5/*6*, however, these findings have not resulted in any recommendations for dosage adjustments thus far.[58,60,61] While there are no specific guidelines recommending altering duloxetine therapy, it is prudent to consider the metabolic implications when using duloxetine for the treatment of OA, especially in individuals with CYP2D6 PM status. Patients may be more likely to experience ADRs and require lower starting doses or a slower titration schedule.

2.3.5. Clinical Implication

No current guidelines recommend dose adjustment of duloxetine based on pharmacogenomic data, however, it is established that serum concentrations of duloxetine are altered by genotype of the CYP2D6 enzyme.[57,58] CYP2D6 PMs have increased drug exposure, whereas ultrarapid metabolizers (UM), defined as having more than one copy of the (normal metabolizer) NM allele (*1/*1XN, *1/*2XN, *2/*2XN), may have decreased concentrations.[59] Patients suffering from comorbid depression and OA may find this treatment to be particularly useful, as well as patients with comorbid neuropathic pain. There is a lack of data available to make recommendations on adjusting doses for OA pain treatment based on a patient's CYP2D6 genotype, however, consideration of increased risk for side effects for PM should be considered.

All antidepressants carry the box warning for increased risk of suicide and suicidal ideation. If considering treating OA utilizing duloxetine, mental health assessments and suicide screen should be completed before initiation and routinely as clinically indicated. Additionally, all antidepressants carry the potential to activate mania or hypomania in patients with bipolar disorder; symptoms of mania and hypomania should be screened before initiation, as well as personal and family history of bipolar disorder. Serotonin syndrome is a serious yet rare complication of using serotonergic agents. The risk is increased if using multiple serotonergic agents concomitantly, or when using medications that impair the metabolism of serotonin. Concomitant use of monoamine oxidase inhibitors is contraindicated with any SNRIs.[56]

Special consideration should be made for patients with underlying hepatic dysfunction, high alcohol intake, and cardiac complications. Patients at risk for seizure should use duloxetine with caution. If a patient has an underlying seizure disorder that is controlled, duloxetine can be considered.[56]

SNRIs have been linked to an increase in blood pressure and heart rate, and duloxetine specifically has a risk of hepatoxicity.[56] Alcohol intake, LFTs, blood pressure, and renal function should be monitored routinely to ensure safe prescribing of duloxetine. Patients with chronic liver diseases and known high alcohol intake should avoid the use of duloxetine if possible. Patients with baseline orthostasis or autonomic dysfunction may be at increased risk for worsening of these symptoms when using duloxetine.[41]

Hyponatremia may occur as a result of treatment with duloxetine, likely related to the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[56] Geriatric patients, patients taking diuretics, or volume-depleted patients may be at higher risk as they are already at risk for hyponatremia at baseline.[62] In clinical trials, geriatric patients, over the age of 65 were included and overall, no difference in safety or efficacy was seen.[56] If symptoms such as nausea, vomiting, fatigue, headache, muscle cramps or altered mental status occur after initiation of duloxetine serum sodium levels and renal function should be assessed.[62] Some experts suggest monitoring serum sodium anywhere from one to four weeks after initiation in high-risk populations.[63,64] Although no overall difference in safety was seen in geriatric patients in clinical trials, there are numerous case reports of SIADH as a result of duloxetine therapy with varying onset.[65,66] Per FDA labeling, dosage adjustments based on adult age are not necessary.[56]

While duloxetine can be an effective medication to manage multiple pain conditions, it is important to note the potential for withdrawal effects upon discontinuation. The degree of discontinuation syndrome a patient may experience is typically related to the dose and duration of

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therapy. The larger the dose and the longer the patient has been taking the medication, the more likely they are to experience discontinuation side effects. The abrupt discontinuation of duloxetine is not recommended if avoidable.[56]

2.4. Tramadol

2.4.1. Pharmacotherapy

Tramadol is a synthetic opioid used for moderate to severe acute and refractory pain.[67] It is also a reuptake inhibitor of both serotonin and norepinephrine.[67] Tramadol differs from other opioid medications in its potency, it is considered the least potent opioid medication due to its binding affinity for μ-opiate receptors.[68] ACR guidelines conditionally recommend tramadol for the treatment of OA pain, it may be useful for patients with contraindications to NSAIDs, who have failed other treatment and who may not be surgical candidates.[7] Data shows that opioids of any kind provide effective acute pain management; however, they only provide a modest benefit for long-term use and possess significant long-term and short-term safety concerns. Randomized controlled trials have not addressed the use of tramadol or other opioids for long-term use, past 12 months, leaving unanswered questions about the long-term efficacy and safety of tramadol in OA treatment. Abuse, misuse, and risk of overdose are among those safety concerns garnering tramadol's controlled substance drug status. Tramadol also possesses significant potential for adverse effects, including constipation, respiratory depression, and CNS depression.[69]

2.4.2. Mechanism of Action

Tramadol is a centrally acting agonist of μ-opioid receptors with SNRI properties and structural similarities to morphine and codeine.[67] Tramadol also binds to κ- and δ-opioid receptors, albeit weakly. In comparison to morphine, tramadol has a 6,000-fold lower affinity to the μ-opioid receptor.[67] Tramadol is a racemic mixture of two active enantiomers, each of which has analgesic properties via differing mechanisms. The (+)-tramadol enantiomer and its active metabolite (+)-*O*-desmethyl tramadol (M1) bind to μ-opiate receptors in the central nervous system (CNS), resulting in inhibition of the ascending pain pathway.[67] In addition, this enantiomer functions as a serotonin reuptake inhibitor. The M1 metabolite notably binds much more potently to μ-opiate receptors. The (-)-tramadol enantiomer inhibits norepinephrine reuptake, providing synergistic analgesic effects through the descending pain pathway. [67]

2.4.3. Clinical Pharmacology

Tramadol is extensively metabolized in the liver by CYP3A4 and CYP2D6. CYP2D6 converts tramadol into its active metabolite *O*-desmethyl tramadol (M1), while CYP3A4 metabolizes it into *N*-desmethyl tramadol (M2), an inactive metabolite.[67] The primary metabolic pathway involves *O or N*-demethylation, glucuronidation, and sulfation in the liver. Tramadol is excreted renally in the urine with about 60% as metabolites, and 30% as the unchanged parent drug.[68] Two formulations of tramadol are available, immediate release (IR) and extended release (ER), which differ in their onset, duration, and elimination profiles.

Tramadol IR formulation typically has an onset of effect within one hour of ingestion, with a peak plasma level of tramadol and M1 at 2-3 hours.[70] With four times daily dosing, steady state of both tramadol and M1 is typically achieved within two days of therapy.[70] The IR formulation has a duration of action of around 4-6 hours, while the ER formulation has a duration of action of about 24 hours. Tramadol ER has a peak plasma level between 4-12 hours and M1 at 5-15 hours.[69] The IR formulation has an elimination half-life of about 6 hours (tramadol) and 7 hours (M1), while the ER capsule is about 10 hours (tramadol) and 11 hours (M1).[70] The tramadol ER tablet has an elimination half-life of about 8 hours (tramadol) and about 9 hours (M1).[69]

 doi:10.20944/preprints202505.0436.v1

2.4.4. Pharmacogenomics

Tramadol has established guidelines for use based on CYP2D6 phenotype.[71,72] Tramadol's main metabolic pathway is via CYP2D6, which is involved in the conversion of (+)-tramadol to the active M1 metabolite. [67] Individuals with CYP2D6 PM will have increased plasma concentration of tramadol by up to 20% and decreased levels of the active M1 metabolite, resulting in less potent analgesic effects. Individuals with CYP2D6 UM will experience more potent analgesia as a result of increased exposure to the active M1 metabolite. Patients with CYP2D6 UM status can have severe respiratory depression and increased mortality as a result of toxic levels of the M1 metabolite. CYP3A4 metabolism results in the M2 metabolite, which exhibits no pharmacological activity.[72,73] See Table 3 for CPIC tramadol dosing recommendations based on CYP2D6 phenotype. [72]

Table 3. CPIC Dosing Recommendations for Tramadol based on CYP2D6 Phenotype (Crews et. al, 2021).

CYP2D6 Phenotype	Activity Score	Recommendation	Classification of Recommendation
Ultra rapid metabolizer	>2.25	Avoid use of tramadol due to the risk of toxicity; use a non-codeine opioid if therapy is necessary	Strong
Normal metabolizer	1.25-2.25	Metabolism is as expected, utilize dosing per label recommendations	Strong
Intermediate metabolizer	0 to <1.25	Utilize dosing per label recommendations. If diminished response, consider an alternative opioid	Optional
Poor metabolizer	0	Avoid tramadol due to diminished analgesic effect	Strong

2.4.5. Clinical Implications

Tramadol may be a useful option for pain management in patients with OA, but it should be used with careful consideration. In general, the CDC recommends against the use of any opioids for long-term pain control due to limited evidence for long-term benefit and safety concerns.[74] Patients taking other CNS depressants such as benzodiazepines, alcohol, sedative hypnotics, should avoid use of tramadol due to increased CNS depression and respiratory depression risk.

Tramadol, unlike other opioid medications, carries a risk for seizure and serotonin syndrome.[70] Caution is warranted in patients with a history of seizures, those taking concomitant medications that lower the seizure threshold, or individuals at elevated risk due to alcohol or benzodiazepine withdrawal. Additional risk factors include CYP2D6 poor metabolizer status and concomitant strong CYP2D6 inhibitors, and serotonergic agents. exercise caution when using tramadol. Like other opioids, tramadol also carries a substantial risk of dose-related adverse effects, including overdose, respiratory depression, and death. [75]

Additionally, tramadol has both hepatic and renal dose adjustments. Patients with severe hepatic dysfunction (Child-Pugh Class C) should not exceed a dose of 50 mg every 12 hours of IR formulation and should not take ER formulation.[69] Patients with CrCl <30 ml/min should not exceed 200 mg of IR formulation per day and should avoid ER formulation. Additionally, it is recommended to start with the IR formulation and reserve the ER formulation for patients who will need therapy exceeding one week. [69]

Older adults aged 65 and older were enrolled in clinical trials for tramadol. In general, opioids can increase fall risk, induce delirium in older adults, and should be used with precautions.[76] As older adults are more likely to have reduced kidney function, drug elimination can be decreased, resulting in increased drug exposure.[70] Per FDA labeling, adults over 75 should not exceed a total daily dose of 300 mg/day, and should not use the tramadol ER formulation. [70]

 doi:10.20944/preprints202505.0436.v1

2.4.6. Future Perspective

The perception and response to pain exhibit considerable interindividual variability, which is influenced by a range of factors. Genetic variation contributes modestly to this variability, accounting for a portion of the differences in pain sensitivity and analgesic response among individuals. The development of chronic pain could be explained by gene and environment interaction, and so are the pain sensitivity and response to analgesics. A large genome-wide association study was conducted to further uncover the link between genetics and multisite chronic pain (MCP) in the UK.[77] The study identified 76 independent single-nucleotide polymorphisms (SNPs) associated with MCP across 39 loci. The identified genes had various functions, but many were related to the nervous system. Another meta-analysis looking at 177,517 patients' genomes with OA uncovered 52 unique risk variants that were not known before.[5] Overall, the analysis uncovered 77 high-confidence OA effector genes that span across joint degeneration, neuronal function, skeletal development, immune response, and inflammation. They further investigated potential drug targets associated with these genes and identified several compounds, including existing disease-modifying anti-rheumatic drugs (DMARDs). Although these drugs are established in the treatment of other inflammatory conditions, there is currently limited evidence supporting their use in osteoarthritis (OA). This finding highlights a promising avenue for future OA therapy and drug development.

Current approaches to fill the gaps in treatment modalities for OA include targeting inflammation suppression, cartilage regeneration, and novel pain control mechanisms. Emerging therapies under investigation for OA pain include **Botulinum Toxin A** and **Resiniferatoxin (RTX),** both of which are currently being evaluated in clinical trials for their efficacy in providing targeted, long-lasting pain relief. [78] Cartilage regeneration may be a potential avenue for OA treatment. The angiopoietin-like 3 (ANGPTL3) signaling pathways are being explored and have been shown to regenerate and preserve cartilage in vivo studies.[78] The STEP-9 trial explored OA knee pain scores to weight loss from semaglutide and found the mean change in WOMAC pain score at week 68 was -14.2 points compared to placebo (P<0.001).[79] Furthermore, a growing number of clinical trials are underway to evaluate the potential effectiveness of various **DMARDs** in OA, which may offer new directions for disease management beyond symptomatic relief.

3. Conclusion

Osteoarthritis continues to impose a substantial burden on millions of individuals due to its chronic nature, absence of curative therapies, and limited individualized treatment options. Older adults are disproportionately impacted by OA, which presents numerous challenges for the optimal management of the disease. Integrating pharmacogenomics into OA management presents an opportunity to refine pain management strategies by aligning drug selection and dosing with a patient's genetic profile. Pharmacogenomic data, particularly for enzymes such as *CYP2D6*, *CYP2C9*, and *UGT1A6*, offer insights that can guide safer and more effective use of analgesics. Although formal OA treatment guidelines are still evolving, current evidence supports the clinical utility of PGx in reducing adverse drug reactions and optimizing therapeutic efficacy. As access to genetic testing becomes more widespread, PGx holds the potential to transform OA care from a one-size-fits-all approach to one that is truly individualized and evidence-based.

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