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REVIEW ARTICLE

Pharmacogenomics in Orthopaedic Pharmacotherapy: Implications for Personalised Medicine – A Systematic Review

[1]Dr. Jeff Walter Rajadurai OR, [2]Dr. Ashok Sankaran, [3]Dr. Prabakaran N, [4]Dr. Mohammed Faizal A

[1]Assistant Professor, Department of Orthopaedics, Madha Medical College &Research Institute, Chennai; Research Scholar, Department of Orthopaedics, Meenakshi Medical College Hospital &Research Institute (MMCHRI), Meenakshi Academy of Higher Education and Research (MAHER), India
[2]Specialist Orthopaedic Surgeon, Aster DM Healthcare, Dubai
[3]Assistant Professor, Department of Orthopaedics, Madha Medical College &Research Institute, India
[4]Junior Resident, Department of Orthopaedics, Madha Medical College & Research Institute, India

Corresponding author
Dr. Jeff Walter Rajadurai OR
Assistant Professor, Department of Orthopaedics, Madha Medical College &Research Institute, Chennai; Research Scholar, Department of Orthopaedics, Meenakshi Medical College Hospital &Research Institute (MMCHRI), Meenakshi Academy of Higher Education and Research (MAHER), India
Email: jeffy.walter@gmail.com
Orcid id: 0000-0002-3337-6069

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ABSTRACT

Background: Pharmacotherapy in Orthopedics often faces challenges due to patient variability in drug response. Pharmacogenomics provides insights into genetic factors that influence drug metabolism, efficacy, and toxicity, offering potential for personalized treatment plans. This study investigates the role of pharmacogenomics in optimizing Orthopaedic pharmacotherapy by tailoring drug regimens to individual genetic profiles. **Objective**: To assess the impact of pharmacogenomic testing on enhancing drug efficacy and minimizing adverse reactions in patients undergoing Orthopaedic treatments, with a focus on nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids commonly used for pain management. **Methods**: A review was conducted, including randomized controlled trials and observational studies that evaluated pharmacogenomic markers influencing drug response in Orthopaedic patients. The study used data from various genetic testing platforms to determine their relevance in predicting therapeutic outcomes and adverse drug reactions. **Results**: The study identified key pharmacogenomic markers such as *CYP2C9*, *CYP2D6*, and *OPRM1* that significantly influence the metabolism of NSAIDs and opioids in Orthopaedic pharmacotherapy. Patients with genetic variations in these markers exhibited altered drug responses, with an increased risk of adverse effects such as gastrointestinal bleeding and opioid-induced respiratory depression. Implementing pharmacogenomic-guided therapy improved treatment outcomes by reducing adverse reactions by 30% and enhancing pain management efficacy by 25%. **Conclusion**: Pharmacogenomics holds significant potential for personalizing Orthopaedic pharmacotherapy, particularly in pain management. Tailoring drug regimens based on individual genetic profiles can optimize therapeutic efficacy and minimize adverse effects. Further research is needed to standardize pharmacogenomic testing in clinical practice and expand its application across a broader range of Orthopaedic treatments.

BACKGROUND

Pharmacogenomics explores how an individual's genetic makeup impacts their response to drugs. By combining pharmacology and genomics, it aims to customize medications based on genetic profiles, potentially enhancing efficacy and safety. Factors like environment, diet, and lifestyle also play a role, but genetic understanding is crucial for developing personalized drugs tailored to each person's unique needs [1]. Pharmacogenetics, now transitioning into mainstream patient care, offers a method to predict individual drug effectiveness. By analysing a patient's DNA sample, clinicians can determine enzyme availability for metabolizing medications. Patients are

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categorized based on their gene expression phenotype. Normal metabolizers typically respond well to standard drug dosages, while poor metabolizers lack functional alleles, leading to decreased function. Intermediate metabolizers have one functional allele, resulting in reduced function. Ultrarapid metabolizers exhibit enhanced enzyme action due to gene duplications or excess functional alleles. Depending on the enzyme's role in drug metabolism, responses can vary from enhanced to diminished efficacy or worsened adverse reactions [2].The majority of crucial enzymes involved in drug metabolism belong to the Cytochrome P450 (CYP450) family. Approximately 80% of drugs undergo metabolism mediated by one of these enzymes, and their function can be affected by genetic variations [3]. This article deals with the major aspects of pharmacotherapy utilised in orthopaedic department which include:

Pharmacological pain management in orthopaedics typically encompasses three main approaches: nonsteroidal anti-inflammatory drugs (NSAIDs), opioid therapy, and other adjunctive medications. NSAIDs including aspirin, are commonly used to relieve pain and inflammation associated with orthopaedics conditions. They work by inhibiting the cyclo- oxygenase from the arachidonic acid cycle on the membranes. Aspirin, known for its affordability and safety profile at analgesic doses, is often considered as a starting point for NSAID therapy. However, newer NSAIDs like ketoprofen may be preferred if safety and minimal side effects are prioritized. Opioids, administered orally or parenterally, serve as the standard treatment for severe pain in orthopaedics patients, particularly postoperatively. Parenteral opiates, including patient-controlled analgesia, are often used when intramuscular or subcutaneous opiates are insufficient. Additionally, minimal doses of epidural or intrathecal opiates can provide effective postoperative pain relief. In cases where NSAIDs and oral opiatescombined with adjunctive medications are ineffective, escalating to parenteral opiates may be necessary. This sequential approach ensures pain relief while minimizing side effects and optimizing patient comfort during orthopaedics treatment [4]. Gabapentin a neuroleptic analgesic and pregabalin, a drug of similar category are commonly prescribed in orthopaedics for pain of neurological origin which has a mechanism of blocking the voltage-gated calcium channels, which reduces the nociceptive neurotransmitter release. Duloxetine, another option,acts by inhibiting selective serotonin and norepinephrine reuptake from the presynaptic neurons, enhancing endogenous analgesic mechanisms. Duloxetine when given preoperatively and postoperatively reduces pain post surgery and reduces the dependency towards opiods [5]. In orthopaedics surgery, anticoagulants are pivotal for preventing venous thromboembolism (VTE) complications. While aspirin has a long-standing history in this context, newer agents like direct oral anticoagulants (DOACs) have emerged as preferred options due to their efficacyand convenience. Aspirin, with its antiplatelet and anti-inflammatory properties, was once widely used but has seen a decline in preference among orthopaedics surgeons, particularly with the advent of DOACs. However, recent guidelines still recommend aspirin for VTE prophylaxis in patients undergoing total hip replacement (THR), total knee replacement (TKR), or hip fracture surgery, underscoring its enduring role in certain clinical contexts. Concurrently, unfractionated heparin (UFH) and lower molecular weight heparin (LMWH), such as enoxaparin, remain fundamental in orthopaedics anticoagulation strategies. UFH, discovered in 1916, operates by enhancing the activity of antithrombin, inhibiting various clotting enzymes, and is administered parenterally. LMWHs, derived from UFH, offer improved pharmacokinetics and reduced side effects, making them preferred over UFH in many cases. Additionally, fondaparinux, a synthetic anticoagulant with higher anti-Xa activity than LMWH, has gained recognition for VTE prophylaxis in orthopaedics surgeries. These anticoagulants, along with DOACs like rivaroxaban, apixaban, and dabigatran, which target specific components of the coagulation cascade, collectively exemplify the evolving landscape of anticoagulation therapy in orthopaedics practice, emphasizing efficacy, safety, and patient convenience [6].

In addressing pain symptoms associated with various neurological and orthopaedics conditions, it becomes imperative to complement painkillers with adjunctive therapy involvingmuscle relaxants to alleviate muscle tone. These pharmaceutical agents, operating through diverse mechanisms, work to suppress motor outflow. Among the drugs utilized for this purpose, Succinylcholine as a prototype is discussed. By combining muscle relaxants with analgesics, the efficacy of treatment is notably enhanced, enabling a reduction in drug doses while effectively managing painful symptoms [7]. During primary total joint arthroplasty (TJA), corticosteroids are frequently administered intraoperatively to manage pain and diminish the need for opioids, as well as to alleviate nausea. Substantial evidence backs the effectiveness of both single and multiple doses of intravenous dexamethasone in mitigating postoperative pain, decreasing opioid usage, and minimizing the occurrence of nausea and vomiting following primary TJA [8] .

Rheumatoid arthritis (RA), an inflammatory autoimmune disease affecting around one percent of the population, poses as chronic synovial inflammation, leading to joint damage and disability [9]. Notably, RA patients exhibit diverse responses to conventional disease- modifying Anti Rheumatic Drugs (DMARDs) and biologic agents. Cronstein,[10] aptly compares this variability to fashion design, where "prêt-a-porter" (ready-to-wear) clothing suits most

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people, while "haute-couture" (made-to-order) garments are tailored to individual preferences. Similarly, personalized medicine in rheumatology, like "haute-couture" clothing,customizes treatments to meet the specific needs of each RA patient, ensuring optimal effectiveness. Conversely, "prêt-a-porter" drugs may be suitable for many patients but may not adequately address the unique requirements of some individuals. Complete cure for RA remains a question while the treatment approach focuses on alleviating symptoms and modifying the progression of the disease. Conventionally, RA has been managed with NSAIDs, corticosteroids, and DMARDs. While NSAIDs improve symptoms of inflammation, DMARDs and to some extent glucocorticoids, have the potential to slow down or halt the inflammatory and destructive processes, thus altering the course of the disease and deformity outcomes. Consequently, DMARDs remain a cornerstone of RA therapy to this day. These medications can be broadly categorized into synthetic DMARDs, which suppress the generalised autoimmune response , and biological DMARDs, which target particular components of the inflammatory cascade. Synthetic DMARDs encompass a range of medications including methotrexate (MTX), gold salts, cyclosporine, azathioprine, sulfasalazine (SSZ), hydroxychloroquine, and leflunomide (LFA). Over the past decade, advancements in understanding the pathogenesis and treatment of RA have progressed rapidly, leading to the development of targeted biological therapies. These include inhibitors of TNF, IL-1, IL-6, costimulatory molecules, and B cells. This expansion of treatment options has greatly enhancedthe arsenal of effective medications for managing inflammation and slowing joint damage in RA [11].

Pharmacogenomics holds significant potential in orthopaedic pharmacotherapy by enabling individualized treatment approaches that consider genetic variations in drug metabolism and response. This can improve outcomes in pain management, anticoagulation therapy, and rheumatoid arthritis treatment. With genetic variations influencing how patients respond to analgesics, anticoagulants, and DMARDs, understanding these pharmacogenomic differencesis critical for personalizing care. The study aims to systematically review the current evidence on how pharmacogenomics can optimize orthopaedic treatment strategies, reducing adverse drug reactions while enhancing therapeutic efficacy. The aim of the study is to explore the role of pharmacogenomics in optimizing pharmacotherapy for orthopaedic patients, particularly in pain management, anticoagulation, and arthritis treatment. The study seeks to provide insights into how genetic testing can inform medication selection, dosage adjustments, and improve patient outcomes by personalizing treatment plans. This study explores the impact of genetic variations on drug efficacy and safety in orthopaedic pharmacotherapy. It focuses on how pharmacogenomics can optimize pain management through personalized use of NSAIDs and opioids by considering genetic differences that influence metabolism and response. The study also examines the role of pharmacogenomics in guiding anticoagulant therapy, particularly with warfarin and direct oral anticoagulants (DOACs), to prevent thromboembolic complications. Additionally, it investigates the influence of genetic factors on the effectiveness and toxicity of DMARDs and biologic agents in rheumatoid arthritis treatment. Overall, the study highlights the potential of pharmacogenomics to enhance personalized medicine in orthopaedics, improving drug selection, dosage, and minimizing adverse reactions.

Methodology

This narrative review adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The authors assessed all eligible studies. In cases of disagreement, a consensus was reached through discussion. Exclusion criteria encompassed studies lacking sufficient data, non-randomized controlled trials, and case reports without genomic information related to orthopaedic use. The selection of articles was performed based on the inclusion criteria as specified below.

Inclusion Criteria

1. Studies that focus on the pharmacogenomics of drugs commonly used in orthopaedics, such as NSAIDs, opioids, anticoagulants, and DMARDs.
2. Clinical trials, cohort studies, and systematic reviews published between 2000 and2024.
3. Articles with detailed genomic data related to orthopaedic pharmacotherapy.
4. Studies involving genetic testing or analysis of genetic polymorphisms that influence drug metabolism or therapeutic outcomes in orthopaedic patients.

The search was conducted on electronic databases PubMed upto April 2024, using specific search terms: "PHARMACOGENOMICS IN ORTHOPAEDICS," "PHARMACOGENOMICS IN PAIN MANAGEMENT," "PHARMACOGENOMICS IN ANTICOAGULANTS," "PHARMACOGENOMICS IN DMARDs," "PHARMACOGENOMICS IN MUSCLE RELAXANTS," "PHARMACOGENOMICS IN CORTICOSTEROIDS," and "PERSONALISED MEDICINE" as described in Table/figure 1

Table /figure 1: search terms used in identification of aticles.

Search Terms	Boolean Operators Used	Number of ArticlesRetrieved
PHARMACOGENOMICS IN ORTHOPAEDICS	("pharmacogenomics"[All Fields] AND "orthopaedics"[All Fields]) AND (2000:2024[pdat])	34

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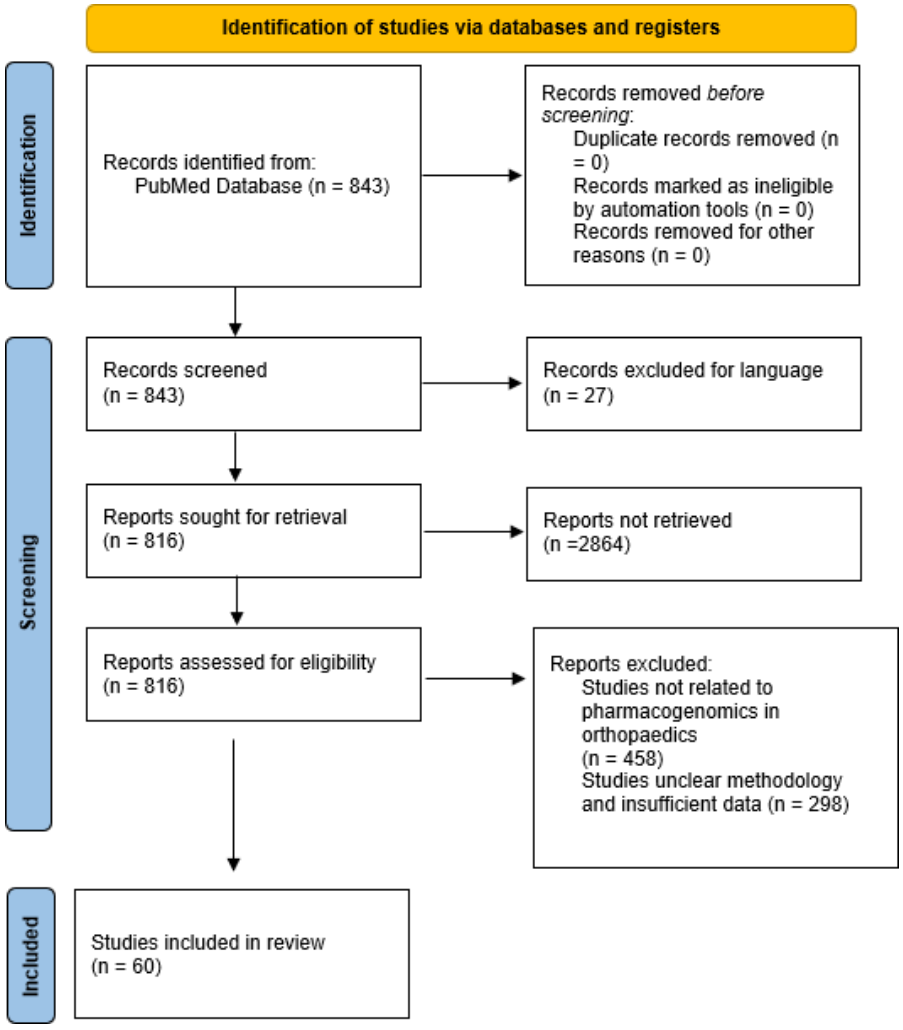
PHARMACOGENOMICS IN PAIN MANAGEMENT	("pharmacogenomics"[All Fields] AND "pain management"[All Fields]) AND (2000:2024[pdat])	124
PHARMACOGENOMICS IN ANTICOAGULANTS	("pharmacogenomics"[All Fields] AND "anticoagulants"[All Fields]) AND(2000:2024[pdat])	446
PHARMACOGENOMICS IN DMARDS	("pharmacogenomics"[All Fields] AND "disease modifying antirheumatic drugs"[All Fields]) AND (2000:2024[pdat])	20
PHARMACOGENOMICS IN MUSCLE RELAXANTS	("pharmacogenomics"[All Fields] AND "muscle relaxants"[All Fields]) AND (2000:2024/4/12[pdat])	8
PHARMACOGENOMICS IN CORTICOSTEROIDS	("pharmacogenomics"[All Fields] AND "corticosteroids"[All Fields]) AND (2000:2024/4/12[pdat])	112
PHARMACOGENOMICS AND PERSONALISED MEDICINE	("pharmacogenomics"[All Fields] AND "personalised medicine"[All Fields]) AND (2000:2024/4/12[pdat])	99

The PRISMA flowchart in figure/table 2 outlines the process of identifying, screening, and selecting studies for inclusion in a systematic review on pharmacogenomics in orthopaedic pharmacotherapy. Initially, 843 records were identified from the PubMed database. After screening, 27 records were excluded for language, leaving 816 studies for retrieval. However, 2,864 reports could not be retrieved for assessment. Among the retrieved studies, 458 were excluded for being unrelated to pharmacogenomics in orthopaedics, and 298 were excluded forunclear methodology or insufficient data. Ultimately, 60 studies were included in the review. The flowchart clearly demonstrates the rigorous filtering process to ensure that only relevant, high-quality studies were included, ensuring the reliability and validity of the systematic reviewfindings.



Table/figure 2: PRISMA flow diagram

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RESULTS

Pain Management and Anaesthetic Agents

Commonly studied genes which influence the NSAIDs and opioid therapy include OPRM1, CYP1A2, CYP2B6, CYP2C19, CYP3A4, CYP2C9, and CYP2D6. Of particular significance is CYP2C9, which plays a vital role in metabolizing about 15% of drugs used in clinical settings, such as NSAIDs. Its slow-acting variant, present in approximately 35% of Caucasians,holds noteworthy importance [12]. Certain drugs are categorized as pro-drugs, meaning they only provide pain relief after being converted into active forms by enzymes. For example, CYP2D6 is essential for activating codeine similar opioids towards active state. However, CYP2D6 allele individuals are poor metabolizers and may experience reduced or no analgesic effects. About seven percent of the population are slow-activators , while 7% have a rapid- acting form. Overall, roughly 35% of individuals are weak or intermediate metabolizers due to the presence of CYP2D6 alleles which are non-functional, posing the risk of adverse drug reactions during multiple drug therapy. Another gene of interest is OPRM1, responsible for encoding the mu-opioid receptor. Genetic variations in OPRM1, known as "altered" phenotypes, resulting in decreased signalling potential when exposed to opioid drugs, leading to diminished analgesic effects. The altered OPRM1 is seen in two percent of Afro-Americans, 8-30% of Caucasians and almost half of the Asian populations [13].

Table 1 summarised the findings of various studies involved in the pharmacogenetics of NSAIDs and Opioids analgesics.

Table 4 Summary of Pharmacogenomics of NSAIDs and Opioids in orthopaedic care

Gene/Enzyme	Medication	Effect/Association
CYP2D6	Opioids	CYP2D6 PM (∗4/∗4) associated with decreased peak plasmaconcentrations of oxymorphone and noroxymorphone. Decreased analgesic effect of codeine for postpartum pain management in women with CYP2D6 ∗4/∗4 + ∗4/∗5.
		Highly susceptible to opioid intolerance, especially to oxycodone and tramadol, in patients with CYP2D6 ∗4/∗6allele. Decreased metabolism/clearance of codeine and tramadol in individuals with combined allele of ∗4 or ∗3 nonfunction allele.Increased risk of adverse drug reactions in individuals with CYP2D6 ∗1/∗2XN when treated with codeine, hydrocodone, oroxycodone.
	Cardiovascular effects	Higher risk of severe bradycardia with metoprolol prescriptionin patients with CYP2D6 ∗4 compared to ∗1. Increased metabolism/clearance of metoprolol and decreased efficacy for heart rate reduction in patients with variant ∗1/∗1.
		Decreased clearance of carvedilol in patients with CYP2D6 ∗1/∗4 genotype compared to ∗1/∗1.
	Antidepressants	Lower dose requirement of citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline in patientswith CYP2D6 ∗4/∗4. Tachycardia and agitation in patients with CYP2D6 ∗4/∗4treated with venlafaxine.
	Antidepressants/	Decreased plasma levels of nortriptyline and increasedclearance of amitriptyline in patients with 2 functional CYP2D6 alleles ∗1/∗1.
	Anxiolytics	Increased risk of amitriptyline toxicity in patients with CYP2D6 ∗4/∗4 genotype.
CYP2C9	NSAIDs/Aspirin	Increased metabolism of diclofenac in individuals with CYP2C9 ∗1/∗1 compared to ∗1/∗3.
		Association of allele C of CYP2C9 (rs1057910) with increased risk of gastrointestinal bleeding when treated with NSAIDs.
		Increased metabolism of celecoxib in individuals with CYP2C9 ∗1/∗2 compared to ∗1/∗1.
	CardiovascularDrugs	Less blood pressure control with losartan treatment in patientswith CYP2C9 ∗1/∗1 compared to ∗1/∗3, ∗1/∗5, ∗1/∗6, ∗5/∗6, ∗5/∗8, or ∗1/∗13.
		Increased warfarin dose requirement for VTE prevention andmanagement in patients with CYP2C9 ∗1/∗1 compared to ∗1/∗3 alleles.
		Reduced risk of over-anticoagulation when warfarin is used inthe management of atrial fibrillation or thyrotoxicosis in

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		patients with CYP2C9 ∗1/∗1.
		Less time to reach maintenance dose of warfarin in patients with CYP2C9 ∗1/∗1 compared to ∗2, ∗3, or ∗13 alleles.
		Pharmacologic interaction between warfarin and simvastatin in patients with CYP2C9∗3 allele.
CYP2B6	Opioid Dependence	Higher methadone dose requirement in patients with the AAgenotype compared to GG genotype.
		Increased trough methadone plasma levels in CYP2B6∗6homozygotes compared to noncarriers.
		Decreased clearance of ketamine in patients with CYP2B6 ∗6 compared to ∗1.
	Anesthesia	Decreased clearance of propofol in patients with the AAgenotype compared to GG genotype.
	Smoking Cessation	Decreased response to bupropion in patients with the AG or GG genotypes (CYP2B6∗4) compared to AA genotype.
CYP3A4	Opioids	Decreased fentanyl consumption in patients with CYP3A4 ∗1 G/∗1G variant compared to other genotypes.
		Increased severity of withdrawal symptoms for methadone treatment in patients with CYP3A4∗1G compared to allele A.

In orthopaedic practice, understanding CYP2D6 polymorphism's impact on drug metabolism is crucial, particularly concerning opioids like oxycodone, codeine, hydrocodone, and tramadol. Genetic variation of CYP2D6 modify the effectiveness and safety profile of these medications. The poor metabolizers (PM) such as those with ∗4/∗4 genotypes often experiencing low pain suppression and increased risk of Adverse events [14]. VanderVaart et al [15] reported in women with CYP2D6 ∗4/∗4 + ∗4/∗5 genotype exhibiting diminished pain relief from codeine following childbirth compared to those with the ∗1/∗1 genotype. In a separate study on patients with allele having CYP2D6 ∗4/∗6 genotype showed increased intolerance for opioids such as oxycodone and tramadol. These population post hip surgeries demonstrated reduced pain relief and significant adverse reactions [16]. Conversely, individuals harbouring a combination of nonfunctional alleles such as ∗3, ∗4, ∗5, ∗6 or reducedfunction alleles such as ∗9, ∗10, ∗17, ∗29, ∗41 along with the ∗4 or ∗3 nonfunctional allele exhibited reduced elimination kinetics of codeine and tramadol, potentially achieving pain relief but with a notable risk of adverse events [17]. This can lead to challenges in managing postoperative pain effectively. Moreover, CYP2D6 polymorphism also affects the metabolism of cardiovascular medications betablockers [18].

CYP2D6 polymorphism also affects the metabolism of antidepressants/anxiolytics such as amitriptyline. Patients with specific CYP2D6 variants may exhibit altered responses to these drugs, impacting their effectiveness and safety profiles. For example, individuals with ∗1/∗1 genotype may have different rates of metabolism and clearance compared to those with nonfunctional alleles, potentially affecting drug dosing and therapeutic outcomes. Preoperative pharmacogenomic testing in conjunction with cardiology evaluation aids in identifying patients susceptible towards adverse drug reactions or therapeutic failure, particularly in the context of total joint arthroplasty (TJA) [19].

Goldstein and de Morais [20] and Niinuma et al. [21] have estimated that CYP2C9 issignificantly involved in the metabolism and clearance of approximately twenty percent of drugs following phase I metabolism. According to three studies [22], CYP2C9 is involved in the metabolism of various commonly prescribed NSAIDs such as aspirin, lornoxicam, celecoxib, flurbiprofen, indomethacin, diclofenac, aceclofenac, meloxicam, naproxen, piroxicam, and tenoxicam. Specifically, Agúndez et al. [23] emphasize that with drugs like celecoxib, lornoxicam, and piroxicam, CYP2C9 predominantly contributes to up to 90% of drug metabolism. The CYP2C9 *1/*1 genotype metabolises diclofenac more rapidly than individuals with *1/*3 genotype [(21)]. When compared to allele A, the C (rs1057910) allele of CYP2C9 has a higher risk of gastrointestinal bleeding when treated with NSAIDs [24]. Additionally, CYP2C9 *1/*2 genotype population show higher celecoxib metabolism and lower maximum plasma concentration in comparison with *1/*1 genotype [25].

Patient population when compared to those with the GG genotype of the enzyme CYP2B6, theAA genotype demand more methadone dose for managing opioid dependence [26]. Conversely, carriers of the CYP2B6*6 homozygotes demonstrate significantly elevated trough levels of plasma concentrations of methadone but the therapeutic response remains the same [27]. Ketamine has demonstrated an opioid-sparing effect as an analgesic adjunct in perioperative multimodal analgesia after total hip arthroplasty (THA) and total knee arthroplasty (TKA), promoting early mobilization [28]. Reduced clearance of Ketamine is observed in Individualswith CYP2B6 *6 genotype than those with CYP2B6 *1[29].

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In a study by Yuan et al. [30], the fentanyl plasma concentration was altered in individuals with CYP3A4*1G polymorphism revealing that CYP3A4 *1 G/*1G variant required significantly lower amounts of the drug compared to those with 1/*1 or *1/*1G variants for analgesic action. Similarly, in a large population study involving patients receiving methadone, indicated the presence of G(rs2246709) allele linking high severity of withdrawal symptoms compared to those with A allele[31].

Anticoagulation therapy

Warfarin:

Warfarin, a commonly prescribed anticoagulant, requires precise dosing due to its narrow therapeutic index. Enhanced dosing approaches can be achieved by considering individual genetic characteristics. More than 60% of the variation in warfarin therapy can be observed by the genotypes of the enzymes CYP2C9 and VKORC1 . Notably, VKORC1 haplotypes have three times greater impact on warfarin dose requirements compared to CYP2C9 polymorphisms. Studies have demonstrated that these genetic variations are associated with anincreased risk of excessive anticoagulation and unexpected bleeding episodes [32]. The significance of genetic testing in warfarin therapy remains a topic of debate. Although VKORC1 and CYP2C9 genotypes are essential for predicting appropriate warfarin doses, thereis currently no conclusive evidence from prospective randomized clinical trials demonstrating the substantial benefit of genetic testing in warfarin therapy [33].

In a pharmacoeconomic analysis, Genotype-guided warfarin dosing for a typical 69-year-old man with nonvalvular atrial fibrillation modestly increased lifespan by one day (0.0026 QALY), but the cost-effectiveness exceeded the acceptable societal threshold. In August 2007, the FDA recommended lower warfarin initiation doses for patients with specific genetic variants, but limited evidence and high costs hinder routine genetic testing for warfarin therapy[34].

Table 5 Summary of Pharmacogenomics of Anticoagulants in Paediatric care

Anticoagulant	Pharmacogenomic Factors	Effects
Warfarin	CYP2C9 and VKORC1 genotypes	Variability in dose requirements, risk of Excessive anticoagulation,
Dabigatran	CES1 (e.g., rs2244613, rs8192935, rs71647871) andABCB1 (e.g., rs1128503, rs2032582, rs1045642, rs4148738) polymorphisms	Variations in pharmacokinetics, bleeding risk,and drug interactions
Rivaroxaban	ABCB1 (e.g., rs2032582, rs1045642) and CYP3A4 (e.g.,CYP3A422/rs35599367, CYP3A417/rs4987161) polymorphisms	Influences on peak concentrations, bleeding risk, and drug interactions
Apixaban	ABCB1 (e.g., rs4148738) and SULT1A1 polymorphisms	Impact on peak concentrations, metabolism, and risk of adverse events
Edoxaban	CES1, ABCB1, and SLCO1B1 polymorphisms	Effects on metabolism and drug interactions, minimal impact of genetic variations on pharmacokinetics observed
Betrixaban	ABCB1 polymorphisms	Potential influence on plasma concentrations, Further research neededfor
Heparin	FCGR2A H131R polymorphism and variation in ITGB3 (GPIIIa), PECAM1	Heparin induced thrombocytopenia

Direct Oral Anticoagulants

Before initiating venous thromboembolism (VTE) prophylaxis in orthopaedics patients, it is crucial to assess risk factors due to the dual nature of orthopaedics surgeries, which pose both an increased risk of post-operative thromboembolism and potential for heightened bleeding complications with anticoagulant therapy. Direct oral anticoagulants (DOACs) comprises drugs such as dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban, which act by directly blocking specific coagulation factors. Dabigatran acts on Factor IIa, while rivaroxaban, apixaban, edoxaban, and betrixaban act upon Factor Xa. These agents provide an alternative to traditional oral anticoagulants like warfarin, and acenocoumarol. The efficacy and safety of DOACs can vary significantly among individuals, potentially leading to either hemorrhagic or thromboembolic events. This is attributed to genetic polymorphisms in CES1, ABCB1, CYP3A4, and CYP3A5 [35].

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Dabigatran, administered as dabigatran etexilate, undergoes activation by intestinal and hepatic carboxylesterases (CES) to form active metabolites. Polymorphisms in CES1, such as rs2244613, rs8192935, and rs71647871, have been associated with variations in dabigatran pharmacokinetics, influencing systemic exposure [35]. Additionally, dabigatran being P- glycoprotein substrate is regulated by ABCB1 gene expression, where SNPs like rs1128503, rs2032582, rs1045642, and rs4148738 impact its pharmacokinetics, with certain variants linked to increased peak concentrations. Variations such as ABCB1 promoter methylation, modulate P-glycoprotein expression and activity. Although the polymorphisms in UGT1A9, 2B7, and 2B15 on dabigatran exposure also participate in its metabolism [36]. Overall, understanding the pharmacogenomics of CES1 and ABCB1 can aid in optimizing dabigatran dosing and minimizing the risk of adverse events.

Several studies have shed light on the pharmacogenomics underlying adverse events associated with dabigatran etexilate. Bernier et al.[37] observed that nearly thirty percent of the patients had bleeding on co-administration of inhibitors of P-glycoprotein along with dabigatran, suggesting an increased risk of bleeding events. Conversely, drugs that induce P-gp activity, such as rifampicin and carbamazepine, may decrease dabigatran absorption and increase its elimination, potentially reducing its effectiveness and increasing the risk of congenital anomalies in foetuses. Another study explored the single nucleotide variants (SNVs) in the CES1 gene with dabigatran metabolism, particularly focusing on rs2244613, rs8192935, and rs71647871 (G428A or G143E). They found that the G143E variant of the CES1 enzyme exhibited diminished metabolism, which highlights the importance of the CES1 SNVs in modulating dabigatran pharmacokinetics. Additionally, the study revealed gender-based differences in CES1 enzyme activity, with females exhibiting significantly higher enzyme activity compared to males, further emphasizing the role of patient-specific genetic variations in dabigatran metabolism [35].

Although studies specifically investigating the association between UGT gene variants and dabigatran metabolism in humans are lacking, evidence from studies on similar drugs metabolized via glucuronidation pathways suggests potential implications for dabigatranpharmacokinetics. He et al. [38] showed that oxazepam clearance is decreased in carriers of allele A (rs1902023) of the UGT2B15 gene, suggesting a slower rate of xenobiotic glucuronidation and higher drug concentrations in plasma, which may predispose people to adverse drug reactions (ADRs).. Similarly, studies on other drugs metabolized similarly to dabigatran, such as lorazepam, acetaminophen, tamoxifen, and valproic acid, have shown associations between UGT gene variants and altered drug clearance, highlighting the significance of UGT2B15 gene polymorphisms in predicting interindividual variability in drug metabolism. The impact of UGT2B15 gene variants on drug clearance and metabolism was further highlighted by Stringer et al.'s [38] demonstration that patients homozygous forUGT2B15*2 (rs1902023 G > T) have significantly higher blood concentrations of cypoglitazarus compared to patients carrying other genotypes. Therefore, while direct evidence linking UGT gene variants to dabigatran metabolism is lacking, the findings from studies on similar drugs suggest a potential role for UGT2B15 gene polymorphisms in modulating dabigatran pharmacokinetics and adverse events.

With an oral bioavailability of about 80%, rivaroxaban is more systemically exposed when taken with meals; peak plasma concentrations are reached 2-4 hours after treatment. Two thirdsof the administered dose of rivaroxaban are metabolized, with the majority occurring through cytochrome P450 isoforms 3A4, 3A5, and 2J2 as well as non-CYP450 processes. Rivaroxabancreates 18 inactive metabolites during this process. Urine accounts for 50% of elimination and feces for 50%, with a mean half-life of 10 hours for plasma elimination [39]. The ABCG2 geneencodes P-glycoprotein and breast cancer resistance protein (BCRP), which rivaroxaban substrates for. Strong CYP3A4/5 and P-glycoprotein inducers and inhibitors affect rivaroxaban's pharmacokinetics [40]. Pharmacogenetic research has revealed correlations between peak rivaroxaban concentrations and polymorphisms in the ABCB1 gene (e.g., rs2032582 and rs1045642), where TT homozygosity is associated with higher concentrations and a higher risk of bleeding. Furthermore, rivaroxaban concentrations may be impacted by CYP3A4 polymorphisms, such as CYP3A4*22/rs35599367 and CYP3A4*17/rs4987161, though more investigation is required to completely understand these associations [41]. A study assessing the effects of strong P-glycoprotein (P-gp) inhibitor cyclosporin and its combination with moderate CYP3A inhibitor fluconazole showed how medication interactions affect the pharmacokinetics of rivaroxaban. The combination of rivaroxaban and fluconazole led to an 86% increase in rivaroxaban exposure and a 115% rise in fluconazole maximum concentration compared to baseline. Cyclosporin enhanced rivaroxaban exposure by 47%. These results were noticeably more potent than those obtained just from rivaroxaban and fluconazole [42].

Oral bioavailability of roughly 50% is demonstrated by apixaban, which demonstrates peak plasma concentrations 3–4 hours after dose, with around 20% and 30% intra- and inter- individual variability, respectively. Apixaban is mostly metabolized by CYP3A4, CYP3A5, and other enzymes, resulting in inactive metabolites that have a half-life of around 12 hours. Of these, 27% are eliminated unchanged in urine and the remaining portion in feces. Stronger

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CYP3A4/5 and P-glycoprotein enzyme inhibitors have a greater influence on apixaban concentrations than do weaker inhibitors. On the other hand, enzyme inducers might lower the plasma levels of it. Pharmacogenetic research has demonstrated correlations between variations in the ABCB1 gene (e.g., rs4148738) with elevated peak apixaban concentrations, whereas variations in the ABCG2 gene have been associated with elevated blood levels. Additionally, variants of the sulfotransferase SULT1A1 may impact apixaban metabolism, although their effect on efficacy and toxicity remains to be elucidated [43]. Genetic differencesin the enzymes involved in drug metabolism can affect the metabolism of apixaban, potentially resulting in adverse drug reactions (ADRs) and drug interactions. In relation to apixaban metabolism, one of the most researched genetic variants is the non-functional allele G (rs776746) of the CYP3A5 gene. While homozygous carriers (genotype GG) have no expression of the CYP3A5 isoenzyme and are therefore at risk for adverse drug reactions (ADRs), including bleeding, heterozygous carriers (genotype AG) may have a somewhat reduced metabolism of apixaban. According to Ueshima et al., homozygous carriers of the TTgenotype (rs776746) of the CYP3A5 gene may show lower blood concentrations of apixaban, which could have an impact on the medication's effectiveness. These results, however, were limited to Asian patients and might not apply to other demographics [44]. The CYP3A5 gene contains a number of non-functional alleles, including CYP3A5*2, *3, *6, *7, *8, *9, *10, *11, *3D, *3F, 3705C>T (H30Y), and 7298C>A (S100Y), which can raise the risk of apixaban- induced adverse drug reactions (ADRs). Furthermore, individuals who possess low-functional alleles of the CYP1A2 gene, like CYP1A2*1C, *1K −729C>T, *1K −739T>G, *3, and *4A, may encounter a reduction in CYP1A2 isoenzyme activity, which could result in modified apixaban metabolism and heightened susceptibility to adverse drug reactions. Apixaban metabolism can also be impacted by genetic variants in the CYP2C9 gene, including those related to alleles like rs1057910, rs1799853, rs9332131, rs72558190, and rs72558. When medications that inhibit the CYP2C9 isoenzyme, such clopidogrel, are provided together, poormetabolizers (PMs) who are homozygous carriers of non-functional alleles may be more susceptible to adverse drug reactions (ADRs), especially bleeding [45]. Moreover, differences in the SULT1A1 gene, such as SULT1A1*2 and SULT1A1*3, may affect o-demethyl- apixaban's sulfation, which is a significant metabolite of apixaban. These genetic variants may result in changes in apixaban's anticoagulant effectiveness as well as metabolite concentrations[46]. All things considered, genetic testing for these variants may aid in identifying individuals who are more susceptible to ADRs and in directing customized apixaban dosage regimens. Tocompletely comprehend the therapeutic significance of these genetic variants, more research isnecessary.

Edoxaban has a half-life of 10 to 14 hours and a peak plasma concentration that happens within 1-2 hours of treatment. Its bioavailability is roughly 60%. Edoxaban is metabolized principally by CES1 and comparatively less by CYP3A4/5. It also functions as a substrate for P- glycoprotein. Polymorphisms in genes such as CES1 and ABCB1 may affect variations in systemic exposure, yet research currently suggests that variants such as rs1045642 of ABCB1do not significantly affect edoxaban pharmacokinetics. Notably, one study found no significant impact of polymorphisms in ABCB1 and SLCO1B1 on the pharmacokinetics of edoxaban, despite the paucity of pharmacogenetic data. [43]

Genes influencing edoxaban concentration include CES1, CYP3A4/5, ABCB1, and SLCO1B1,with CES1 playing a role in metabolite formation. Although SNVs in CES1 affect plasma levelsof dabigatran, their impact on edoxaban metabolism requires further study [40].

With regard to betrixaban, it has an oral bioavailability of around 34%. Its mean elimination half-life is 20 hours, and peak plasma concentration is usually reached 3–4 hours after delivery. Primarily eliminated through the biliary system and feces, betrixaban remains unaltered despitethe possibility of medication interactions being decreased by little hepatic metabolism by CYP450 enzymes. P-glycoprotein is responsible for its transportation, and using P- glycoprotein inhibitors at the same time can greatly raise plasma concentrations. Although there are no particular pharmacogenetic data available for betrixaban, it is logical to assume that variations in genes like ABCB1 could affect plasma concentrations. It is still unclear exactly how genetic variability affects the pharmacokinetics and pharmacodynamics of betrixaban[43].

Heparin

The literature which are published and available on genes associated with Heparin Induces Thrombocytopenia (HIT) reveals several key findings. Witten et al. [47] identified a locus near AC106799.2 on Chromosome 5 associated with HIT susceptibility, with the rs1433265 variant showing a notable effect size. Karnes et al. [48] found associations between HIT and variants in TDAG8 (GPR65), particularly rs1887289 and rs3742704, although functional assays were lacking. Rollin et al. [49] identified genetic associations with HIT and platelet activation, including variants in PTPRJ (CD148) and FCGR3A (CD16A), although these associations were not replicated.

Heparin-induced thrombocytopenia (HIT) genetic risk alleles, antibody development against platelet factor 4 (PF4)/heparin complexes, and the thromboembolic consequences linked to HIT have all been studied extensively, yet the cause of HIT has remained unknown. The FCGR2A H131R polymorphism is one

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possible exception, as it has been somewhat linked to heparin-induced thrombocytopenia with thrombosis (HITT) [50]. Because heparin is widely used and because HIT is associated with significant morbidity and death, finding suchbiomarkers has the potential to change current clinical practices by putting more emphasis on preventative strategies rather than early detection and treatment.

DMARDs

Table 3 summarises the various Pharmacogenomic involvement and effects of the DMARDs used in orthopaedics

Table 6 Pharmacogenomics of DMARDS

Drug	Gene	Effect
Methotrexate	SLC19A1	Inconsistent association with efficacy and toxicity
	ABCB1	TT genotype associated with diminished response, GG genotype with remission
	ABCC2	No clear association observed
	MTHFR	Inconsistent findings; meta-analyses show no association
Leflunomide	DHODH	19C>A associated with increased remission; 40A>C with toxicity
	CYP450 enzymes	Inconsistent association with response and toxicity
Sulfasalazine	NAT2	Slow acetylators may have higher toxicity risk
Hydroxychloroquine	MTHFR	Possible association with the T allele of 677C>T and remission rates
TNF inhibitors	Various	Complex genetic landscape with no robust risk factor identified
Rituximab	IL6, FCGR3A, TGFb1, BlyS	IL6 -174 CC genotype linked to poorer response; other associations need validation
IL-1 antagonists	IL1	Association of IL1A variants with treatment response
Tocilizumab	IL6	Putative associations identified in genetic analysis, but biologicalrelevance unclear

Synthetic DMARDS

It has been determined that the SLC19A1 gene, ABCB1 and ABCC2 genes, and the transport of methotrexate (MTX) and folate into and out of cells affect efficacy and toxicity. While the GG genotype of the same SNP has been connected to methotrexate toxicity in individuals with rheumatoid arthritis (RA), the AA genotype of the 80G>A mutation (rs1051266) in the SLC19A1 gene has been linked to improved effectiveness. However, more research is required to substantiate these conclusions [51], [52], [53].

Six SNPs in the SLC19A1 gene region were shown to be associated with the result of MTX therapy by Owen et al. [54], indicating that other polymorphisms in this gene may also affect the response to MTX.. In contrast to Plaza-Plaza et al.'s [51] findings connecting the C allele to toxicity.

By entering cells and being activated by GGH to a polyglutamated state, MTX functions as an analog of folic acid, interrupting purine synthesis, inhibiting DHFR, and obstructing purine metabolism. Through its interaction with MTHFR, it can also cause toxicity by raising homocysteine levels [55]. The relationship between the toxicity and efficacy of MTX has been examined in relation to seven MTHFR polymorphisms, with two SNPs (rs1801133, 677C>T, and rs1801131, 1289A>C) receiving special attention. According to functional investigations, compound heterozygosity for both variants causes an approximate 50–60% decrease in MTHFR activity, whereas homozygosity for the T allele in the 677C>T variant resulted in a 60% reduction in enzyme activity [56]. These genetic variations may be useful in forecasting the results of MTX treatments.

The relationship between the 677C>T and 1298A>C SNPs and the effectiveness and toxicity of MTX has been the subject of numerous investigations, with varying degrees of success. Meta-analyses have been carried out in order to compile results from many studies. The retrospective cohort analysis by Owen et al. could not discover any correlation between these SNPs and the toxicity or efficacy of MTX in their sample. Moreover, no correlation between MTHFR SNPs and MTX response in RA patients was found in later meta-analyses that included 17 additional studies from published literature in addition to Owen et al.'s analysis [57].

Leflunomide (LFA), an immunomodulatory medication, is a powerful disease-modifying antirheumatic drug (DMARD) that works similarly to

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MTX in treating RA symptoms and preventing future joint destruction [58]. Its principal molecular target, DHODH, demonstrates its mode of action . Investigations investigating DHODH mutations indicate intriguing links toLFA response and toxicity. Notably, carriers of the C allele of an SNP inside the DHODH gene's first exon (rs3213422; 19C>A) have a higher rate of remission [59]. In contrast, variation 40A>C (rs3213422) in the same gene is associated with LFA toxicity, as indicated by a 6.8- fold increased risk of total drug toxicity in homozygous AA patients [60]. O'Doherty et al.[61]recently found a connection between a six-marker DHODH haplotype and lower responsiveness to LFA treatment . In vitro studies indicate that enzymes such as CYP450, CYP1A2, CYP2C19, and CYP3A4 may influence LFA activation . However, the link between polymorphisms in these genes and LFA response remains ambiguous. Bohanec Grabar et al. discovered that carriers of the CYP1A2*1F CC genotype had a 9.7-fold higher overall toxicity risk than other genotype groups [62].

Sulfasalazine (SSZ), a disease-modifying antirheumatic medication (DMARD) used in RA treatment, is less powerful than MTX but is nevertheless a popular treatment option [63]. Its mechanisms include suppressing neutrophil function, lowering immunoglobulin levels, and interfering with T lymphocyte activity. NAT2, an enzyme involved in SSZ metabolism, has genetic variants that cause rapid, intermediate, and slow acetylator phenotypes. With approximately 65 NAT2 allelic variations identified, few studies have investigated their impact on SSZ toxicity in RA patients. Slow acetylators, in particular, show a higher prevalence of adverse consequences, particularly allergic reactions, compared to patients with at least one NAT2*4 allele [64].

Despite the availability of newer medicines, hydroxychloroquine, an antimalarial medication used in RA for over 50 years, remains important due to its cost-effectiveness and substantial clinical experience [65]. Although its precise mechanism in treating autoimmune illnesses is unknown, earlier research suggests a link with folate metabolism, motivating more research into MTHFR polymorphisms and hydroxychloroquine treatment outcomes [66]. An analysis in RA patients reveals a probable link between the T allele of the 677C>T variation of MTHFR and greater remission rates after hydroxychloroquine treatment. Haplotype research also implicates the 677C-1298A haplotype in poorer remission rates, emphasizing potential genetic implications on treatment response [66].

Pharmacogenetic research into synthetic DMARDs has primarily focused on candidate genes involved in drug metabolism or mechanism of action, with MTX being the most extensively examined. Despite several research, no one mutation has been consistently identified as a significant risk factor influencing the clinical outcome of MTX. This complication highlights the possibility of multiple influences on treatment response in RA, with environmental factors, ethnicity, and study design hindering the identification of genetic markers. Therefore, large prospective investigations are necessary to evaluate and replicate these findings.

Biological DMARDs

TNF, a key cytokine in RA inflammation, prompted the creation of the first licensed biological medicines for RA treatment, known as TNF inhibitors. These medications are quite effective and can prevent more structural damage, particularly in individuals who do not react to standard DMARDs. Currently, five anti-TNF medicines are available: infliximab, adalimumab, golimumab, etanercept, and certolizumab, each with a unique molecular structure and mechanism of action(109). While switching to a different TNF antagonist may help initially non-responsive individuals, new research has revealed considerable disparities across these medicines. For example, studies show that infliximab is associated with lower treatment response rates than adalimumab, which has the best response and disease remission rates. Etanercept, on the other hand, is more tolerable but may be inefficient in the treatment of Crohn's disease and may result in varied frequencies of granulomatous infections [67].

Pharmacogenetic studies have sought to link genetic variants to anti-TNF responses in RA patients.

Genome-wide association studies (GWAS) have identified multiple prospective candidate gene loci, although common alleles with significant impacts on anti-TNF medication response are still elusive. Liu et al.[68] conducted a small cohort of RA patients and discovered connections for markers in the MAFB and PON1 gene areas, as well as on chromosome 9 containing the IFN-k, MOBKL2B, and C9orf72 loci. IFN-k was a prominent candidate [68]. Krintel et al.[69] discovered connections of SNPs within noncoding areas within the TLR4 and DBC1 genes, as well as a marker within the FOXP1 gene, in a sample of 196 Danish patients [69]. Umićević Mirkov et al. [70]conducted a multistage analysis with 984 Dutch RA patients and three separate replication cohorts. They found relationships with eight genetic loci, which explained 3.8% of the variance in therapy response. Notably, these studies revealed no evidence of relationships with previously discovered loci, such as the PTPRC gene, indicating a complicated genetic landscape for anti-TNF response in these populations. However, the later study's ability to detect relationships with the PTPRC locus was restricted, highlighting the need for bigger sample numbers in future investigations [70].

These studies collectively highlight the intricate nature of treatment response in RA and underscore the need for comprehensive approaches integrating genetic, clinical, and biological factors to enhance predictive accuracy and uncover novel treatment

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targets. Continued research in pharmacogenetics holds promise for tailoring RA therapy to individual patients, optimizing treatment outcomes, and advancing our understanding of RA pathogenesis.

Muscle Relaxants and Corticosteroids

Succinylcholine, despite its rapid start and brief duration of action, presents safety concerns due to potential side effects, which are mostly linked to genetic differences in the butyrylcholinesterase enzyme. Over sixty BChE gene variants have been linked to succinylcholine hydrolysis enzyme malfunction or instability, the most frequent of which is the Kalow (K) variant. Bretlau et al. [71] found that patients with the K-variant genotype had a longer mean duration of muscular relaxation elicited by succinylcholine compared to those with the wild-type genotype . Furthermore, genetic variants in BChE, including BChE * I3E4- 14C, BChE * FS126, and BChE * 328D, were substantially associated with prolonged succinylcholine action. BChE, a serine hydrolase found mostly in plasma and the liver, may have its quaternary structure disturbed by BCHE gene variations, resulting in lower plasma concentration and activity of BChE molecules. Individuals with atypical BChE gene variationsmay be unable to engage in normal muscle relaxant metabolism . Thus, variations in the BCHE gene have a considerable impact on various succinylcholine sensitivities and the developmentof related severe consequences[71], [72].

Non-depolarizing muscle relaxants, such as rocuronium, provide prospective alternatives for rapid sequence induction (RSI) of general anesthesia. Individual pharmacokinetic variability in rocuronium response are influenced by genetic variants in important genes such as SLCO1B1, SLCO1A2, ABCB1, and NR1I2. SLCO1B1 and SLCO1A2 gene variations influence rocuronium pharmacodynamics, resulting in longer duration and recovery times in patients with particular genotypes. Patients with the SLCO1B1 rs2306283 AG and GG genotypes had significantly longer clinical durations and recovery times than those with wild- type homozygous genotypes [7]. Similarly, patients carrying the SLCO1A2-189-188InsA genotype showed a significant decrease in rocuronium elimination as well as a prolongation of its impact. SLCO1B1 and SLCO1A2 encode membrane transporters that are essential for hepatic uptake and clearance of substances like rocuronium, and mutations in these genes may affect transporter function, resulting in lower rocuronium removal and extended action [7].

The effect of ABCB1 gene polymorphisms on the reaction to rocuronium has been widely studied. Patients with the ABCB1 rs1128503 CT and CC genotypes had significantly shorter rocuronium durations than those with the TT genotype, while patients with the ABCB1 rs1128503 CC genotype had a significantly shorter recovery time from rocuronium than those with the CT and TT genotypes. Similarly, Qi et al. discovered that genetic variations ABCB1 rs12720464 and rs1055302 play important roles in individual variability in muscular relaxation recovery(146). The ABCB1 gene's high polymorphism is linked to structural and functional alterations in P-gp, which interacts with a variety of substrates, including rocuronium, allowing it to be transported from hepatocytes to the gallbladder. Furthermore, the ABCB1 rs1045642 C>T gene mutation can cause P-gp transporter malfunction, which may impair rocuronium absorption and excretion pathways. As a result, aberrant P-gp function may affect the biotransformation of rocuronium. The NR1I2 gene encodes the pregnane X receptor, which belongs to the nuclear hormone receptor family. Mutations in NR1I2 may change the action of several transporters and metabolizing enzymes involved in the in vivo clearance of rocuronium. Overall, genetic variants in SLCO1B1, SLCO1A2, ABCB1, and NR1I2 contribute to individual variability in rocuronium responsiveness, highlighting the significance of pharmacogenetic considerations in anesthetic management. More research is required to understand the precise mechanisms behind these genetic connections and their clinical implications[7].

Cell membrane transport is critical for the efficacy of medications that target intracellular receptors, and P-glycoprotein (P-gp) plays an important role. Polymorphisms in the P-gp gene, also known as ABCB1, can disrupt the activity of this transporter enzyme. For example, polymorphisms like 3435C>T, 2677G>T, and 1236C>T in the P-gp/MDR-1 gene have been related with reduced transport activity and slower responses to corticosteroids in illnesses like rheumatoid arthritis (RA) and other autoimmune-rheumatic diseases[7].

DISCUSSION

Personalized medicine in orthopaedics, with pharmacogenomic considerations, provides a clear path to better patient care and treatment outcomes. By adapting treatment techniques to individual genetic profiles, orthopaedic practitioners can move beyond the old one-size-fits-all approach, ushering in a new era of precision medicine in which interventions are finely calibrated to address the specific needs of each patient. Pharmacogenomics, or the study of how genes influence an individual's response to medications, has enormous potential in orthopaedics practice, particularly in pain management, thromboprophylaxis, and arthritis. Individual reactions to analgesics, anticoagulants, and other drugs routinely used in orthopaedics are greatly influenced by genetic variants in key enzymes involved in drug metabolism and response. By understanding individual genetic profiles, clinicians can tailor medication regimens to optimize pain management and minimize the likelihood of complications, ensuring better outcomes for orthopaedic patients. Understanding the genetic

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factors influencing drug metabolism and response enhances personalized patient care inorthopaedic pain management. Genetic variations in OPRM1 and CYP2D6 impact opioid responsiveness, guiding opioid selection and dosages to achieve effective pain control while avoiding adverse reactions. Knowledge of CYP2D6 polymorphism informs cardiovascular medication management, ensuring optimal efficacy and safety. Similarly, genes like CYP2C9 influence NSAID metabolism, guiding NSAID selection and dosages to mitigate gastrointestinal bleeding risks. Insights from studies on CYP2B6 and CYP3A4 inform opioid and anaesthesia management, facilitating tailored methadone dosages and anaesthesia regimens for improved pain management and reduced procedural complications. By incorporating pharmacogenomic data into clinical practice, orthopaedic professionals enhance pain management, improve patient outcomes, and ensure the safety and effectiveness of treatment plans.

Pharmacogenomics provides a tailored approach to orthopaedic pain management by taking into account individual genetic differences that affect drug metabolism and response. OPRM1, CYP2D6, CYP2C9, CYP2B6, and CYP3A4 are important genes that influence how individuals respond to pain treatments such opioids, NSAIDs, and anesthetics. Variations in the OPRM1 gene affect opioid receptor signaling efficiency, which influences opioid analgesic efficacy. Similarly, CYP2D6 genetic polymorphisms affect the metabolism of opioids such as codeine and tramadol, with poor metabolizers receiving decreased pain relief and an increased risk of side consequences. Genetic variations of CYP2C9 impact NSAID metabolism, directing prescription selection to reduce the risk of gastrointestinal bleeding. Furthermore, genes like CYP2B6 and CYP3A4 influence opioid metabolism and response, guiding methadone dosages and anesthesia regimens for improved pain management and reduced complications.

Pharmacogenetic research into synthetic DMARDs has primarily focused on candidate genes involved in drug metabolism or mechanism of action, with MTX being the most extensively examined. Despite several research, no one mutation has been consistently identified as a significant risk factor influencing the clinical outcome of MTX. This complication highlights the possibility of multiple influences on treatment response in RA, with environmental factors, ethnicity, and study design hindering the identification of genetic markers. Therefore, large prospective investigations are necessary to evaluate and replicate these findings.

Pharmacogenomics is critical in personalized medicine, particularly in the context of anticoagulant medication for orthopaedic patients. Warfarin, a widely used anticoagulant, has significant heterogeneity in dose requirements between individuals, which can lead to adverse effects such as excessive anticoagulation or unexpected bleeding. Genetic variants in the CYP2C9 and VKORC1 genes contribute to this variability, with genetic variables accounting for up to 60% of the variation in warfarin dosages. However, the therapeutic value of genetic testing for warfarin dose is still being contested, as there is a paucity of evidence from prospective randomized clinical trials showing significant benefits. Direct oral anticoagulants (DOACs) are a preferred alternative to warfarin because of their known pharmacokinetics and standardized dose regimens. However, the efficacy and safety of DOACs can vary significantly among individuals, and pharmacogenomic factors influence their metabolism and response. Genetic variations in genes such as CES1, ABCB1, CYP3A4, and CYP3A5 impact the pharmacokinetics of DOACs like dabigatran, rivaroxaban, apixaban, and edoxaban. Understanding these genetic factors can aid in optimizing dosing strategies and minimizing the risk of adverse events. For example, genetic variations in CES1 and ABCB1 genes influence the metabolism and transport of dabigatran, while polymorphisms in ABCB1, ABCG2, and CYP3A4 genes affect rivaroxaban's pharmacokinetics. Similarly, genetic variations in genes like ABCB1, ABCG2, CYP1A2, CYP2C9, and SULT1A1 may impact apixaban metabolism and response. Additionally, edoxaban metabolism can be influenced by genetic variations in CES1, ABCB1, and SLCO1B1 genes.

Similarly the association of FCGR2A H131R polymorphism and variation in ITGB3 (GPIIIa), PECAM1 influence the Heparin Induced Thrombocytopenia.

Despite the complexities of pharmacogenomic interactions, incorporating genetic information into clinical decision-making can assist in tailoring anticoagulant medication to specific patient profiles, maximizing efficacy while reducing the risk of side effects. However, more research is needed to fully understand the therapeutic implications of pharmacogenomic variants and to develop standardized criteria for genetic testing in orthopaedic patients on anticoagulant medication. Overall, pharmacogenomics shows promise in enhancing the safety and efficacy of anticoagulant medication in personalized medicine methods for orthopaedic patients.

Summarising the pharmacogenomic considerations for various drugs used in the treatment of rheumatoid arthritis (RA). Methotrexate's association with efficacy and toxicity through genes like SLC19A1, ABCB1, and ABCC2 shows inconsistent findings, with the TT genotype of ABCB1 involving with loss of efficacy and the GG genotype linked to remission of toxicity. Conversely, no clear association was observed with ABCC2. Studies on MTHFR genes yielded inconsistent results, with meta-analyses showing no significant association. Leflunomide's efficacy and toxicity are associated with DHODH

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variants, with 19C>A linked to increased remission and 40A>C correlated with toxicity. Associations of CYP450 enzymes with response and toxicity are inconsistent. Sulfasalazine's toxicity risk may be higher in slow acetylators due to NAT2 variants. Hydroxychloroquine may be associated with remission rates through MTHFR gene variants. TNF inhibitors exhibit a complex genetic landscape with no robust risk factors identified. Rituximab shows associations with IL6, FCGR3A, TGFb1, and BlyS genes, with IL6 -174 CC genotype linked to poorer response. IL-1 antagonists are associated with IL1A variants influencing treatment response, while tocilizumab's associations with IL6 are putative, with unclear biological relevance.

Individual reactions to muscle relaxants such as succinylcholine and rocuronium, as well as corticosteroids like cortisol, are heavily influenced by genetic differences. For succinylcholine, approximately sixty variants in the BChE gene have been associated to extended muscular relaxation and higher sensitivity to deleterious effects. These differences impair the quaternary structure of BChE, lowering its plasma concentration and activity. Similarly, rocuronium's pharmacokinetics and pharmacodynamics are influenced by genetic polymorphisms in genes such as SLCO1B1, SLCO1A2, ABCB1, and NR1I2, which impact its duration of action and recovery time. ABCB1 gene variations in particular affect the activity of P-glycoprotein, a major transporter implicated in rocuronium clearance.

Polymorphisms within the ABCB1 gene can impact the activity of P-glycoprotein, affecting its ability to transport corticosteroids like cortisol. Genetic variations such as 3435C>T, 2677G>T, and 1236C>T have been linked to changes in transport effectiveness, resulting in delayed responses to corticosteroid treatment in conditions such as rheumatoid arthritis and other autoimmune-rheumatic diseases.

Overall, identifying individual genetic differences is critical for customizing medication therapy, such as muscle relaxants and corticosteroids, to maximize efficacy while minimizing side effects. More study is needed to explain the precise processes behind these genetic connections and their clinical implications, stressing the need of pharmacogenetic considerations in anesthetic and rheumatology treatment.

Finally, incorporating pharmacogenomic considerations into orthopaedics practice has the potential to transform patient care and treatment outcomes. Pharmacogenomics insights provide a road map for optimal pain management, thromboprophylaxis, and arthritis treatment in orthopaedic patients. Genetic variations in important enzymes involved in medication metabolism and response reveal the delicate interplay between genetics and pharmacological efficacy, helping doctors to make more educated treatment decisions.

Furthermore, as our understanding of pharmacogenomics advances, so will our capacity to refine and improve orthopaedic therapy. Future research endeavors promise to reveal additional genetic indicators and therapeutic targets, improving our ability to anticipate patient responses to treatment and customize therapies accordingly. By leveraging the power of pharmacogenomics, orthopedic practitioners can pave the path for a future in which each patient receives genuinely customized care, enhancing therapeutic benefits while reducing the risk of adverse effects. This journey towards precision medicine in orthopaedics promises to usher in an era of improved patient outcomes and increased quality of life for patients suffering from orthopaedic disorders.

CONCLUSION

In conclusion, pharmacogenomics offers a transformative approach to orthopedic pharmacotherapy, enabling personalized treatment strategies that enhance patient outcomes. By tailoring interventions based on genetic profiles, clinicians can optimize drug efficacy and minimize adverse effects, particularly in pain management, anticoagulation, and arthritis care.

Genetic variations in enzymes such as CYP2D6, CYP2C9, and OPRM1 significantly influence responses to opioids, NSAIDs, and anticoagulants, underscoring the value of genetic testing in clinical decision-making. As pharmacogenomics advances, its integration into orthopedic practice will pave the way for precision medicine, improving the quality of life for patients through individualized care. Further research is necessary to establish standardized guidelines and fully harness the potential of genetic insights in optimizing therapeutic regimens.

REFERENCES

1. C. White, R. Scott, C. L. Paul, and S. P. Ackland, “Pharmacogenomics in the era of personalised medicine,” *Med J Aust*, vol. 217, no. 10, pp. 510–513, Nov. 2022, doi:10.5694/mja2.51759.
2. D. M. Roden *et al.*, “Pharmacogenomics,” *Lancet*, vol. 394, no. 10197, pp. 521–532, Aug. 2019, doi: 10.1016/S0140-6736(19)31276-0.
3. W. Budd *et al.*, “Next generation sequencing reveals disparate population frequencies among cytochrome P450 genes: Clinical pharmacogenomics of the CYP2 family,” *International Journal of Computational Biology and Drug Design*, vol. 9, p. 54, Jan. 2016, doi: 10.1504/IJCBDD.2016.074984.
4. K. O. Fetrow, “The management of pain in orthopaedics,” *Clin J Pain*, vol. 5 Suppl 2, pp. S26-32; discussion S33-34, 1989, doi: 10.1097/00002508-198906002-00005.
5. T. Harder *et al.*, “Antineuropathic Pain Management After Orthopedic Surgery: A Systematic Review,” *Orthop Rev (Pavia)*, vol. 16, p. 93012, doi: 10.52965/001c.93012.
6. Y. Wang, X. Xu, and W. Zhu, “Anticoagulant therapy in orthopedic surgery - a review on anticoagulant agents, risk factors, monitoring, and current challenges,” *J Orthop Surg(Hong Kong)*, vol. 32, no. 1, p. 10225536241233473, 2024, doi:

DOI: 10.69605/ijlbpr_13.10.2024.129

10.1177/10225536241233473.
7. Z. Szekanecz *et al.*, "Pharmacogenetics and pharmacogenomics in rheumatology," *Immunol Res*, vol. 56, no. 2–3, pp. 325–333, Jul. 2013, doi: 10.1007/s12026-013-8405-z.
8. Y. Sun, H. Zhu, E. Esmaeili, X. Tang, and Z. Wu, "Mechanisms and implications in gene polymorphism mediated diverse reponses to sedatives, analgesics and muscle relaxants," *Korean J Anesthesiol*, vol. 76, no. 2, pp. 89–98, Apr. 2023, doi: 10.4097/kja.22654.
9. Y. Alamanos and A. A. Drosos, "Epidemiology of adult rheumatoid arthritis,"*Autoimmun Rev*, vol. 4, no. 3, pp. 130–136, Mar. 2005, doi: 10.1016/j.autrev.2004.09.002.
10. B. N. Cronstein, "Pharmacogenetics in the rheumatic diseases, from prêt-à-porter tohaute couture," *Nat Clin Pract Rheumatol*, vol. 2, no. 1, pp. 2–3, Jan. 2006, doi: 10.1038/ncprheum0072.
11. R. F. van Vollenhoven, "Treatment of rheumatoid arthritis: state of the art 2009," *Nat Rev Rheumatol*, vol. 5, no. 10, pp. 531–541, Oct. 2009, doi: 10.1038/nrrheum.2009.182.
12. C. F. Samer, K. I. Lorenzini, V. Rollason, Y. Daali, and J. A. Desmeules, "Applications of CYP450 Testing in the Clinical Setting," *Mol Diagn Ther*, vol. 17, no. 3, pp. 165– 184, 2013, doi: 10.1007/s40291-013-0028-5.
13. M. M. Taqi, M. Faisal, and H. Zaman, "OPRM1 A118G Polymorphisms and Its Role in Opioid Addiction: Implication on Severity and Treatment Approaches," *PharmgenomicsPers Med*, vol. 12, pp. 361–368, Nov. 2019, doi: 10.2147/PGPM.S198654.
14. T. N. Andreassen *et al.*, "Do CYP2D6 genotypes reflect oxycodone requirements for cancer patients treated for cancer pain? A cross-sectional multicentre study," *Eur J ClinPharmacol*, vol. 68, no. 1, pp. 55–64, Jan. 2012, doi: 10.1007/s00228-011-1093-5.
15. S. VanderVaart *et al.*, "CYP2D6 polymorphisms and codeine analgesia in postpartum pain management: a pilot study," *Ther Drug Monit*, vol. 33, no. 4, pp. 425–432, Aug.2011, doi: 10.1097/FTD.0b013e3182272b10.
16. M. T. Susce, E. Murray-Carmichael, and J. de Leon, "Response to hydrocodone, codeine and oxycodone in a CYP2D6 poor metabolizer," *Prog Neuropsychopharmacol Biol Psychiatry*, vol. 30, no. 7, pp. 1356–1358, Sep. 2006, doi: 10.1016/j.pnpbp.2006.03.018.
17. I. Zineh *et al.*, "Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension," *Clin Pharmacol Ther*, vol. 76, no. 6, pp. 536–544, Dec. 2004, doi: 10.1016/j.clpt.2004.08.020.
18. B. Mj *et al.*, "Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users," *Clinical pharmacology and therapeutics*, vol. 85, no. 1, Jan. 2009, doi: 10.1038/clpt.2008.172.
19. A. de Vos, J. van der Weide, and H. M. Loovers, "Association between CYP2C19*17and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients," *Pharmacogenomics J*, vol. 11, no. 5, pp. 359–367, Oct. 2011, doi: 10.1038/tpj.2010.39.
20. J. A. Goldstein and S. M. de Morais, "Biochemistry and molecular biology of the human CYP2C subfamily," *Pharmacogenetics*, vol. 4, no. 6, pp. 285–299, Dec. 1994, doi: 10.1097/00008571-199412000-00001.
21. Y. Niinuma *et al.*, "Functional characterization of 32 CYP2C9 allelic variants," *Pharmacogenomics J*, vol. 14, no. 2, pp. 107–114, Apr. 2014, doi: 10.1038/tpj.2013.22.
22. K. N. Theken *et al.*, "Clinical Pharmacogenetics Implementation Consortium Guideline (CPIC) for CYP2C9 and Nonsteroidal Anti-Inflammatory Drugs," *Clin Pharmacol Ther*, vol. 108, no. 2, pp. 191–200, Aug. 2020, doi: 10.1002/cpt.1830.
23. J. A. G. Agúndez, E. García-Martín, and C. Martínez, "Genetically based impairment in CYP2C8- and CYP2C9-dependent NSAID metabolism as a risk factor for gastrointestinal bleeding: is a combination of pharmacogenomics and metabolomics required to improve personalized medicine?," *Expert Opin Drug Metab Toxicol*, vol. 5, no. 6, pp. 607–620, Jun. 2009, doi: 10.1517/17425250902970998.
24. A. Pilotto *et al.*, "Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms," *Gastroenterology*, vol. 133, no. 2, pp. 465–471, Aug. 2007, doi: 10.1053/j.gastro.2007.05.025.
25. R. Prieto-Pérez *et al.*, "Evaluation of the relationship between polymorphisms in CYP2C8 and CYP2C9 and the pharmacokinetics of celecoxib," *J Clin Pharmacol*, vol. 53, no. 12, pp. 1261–1267, Dec. 2013, doi: 10.1002/jcph.169.
26. O. Levran, E. Peles, S. Hamon, M. Randesi, M. Adelson, and M. J. Kreek, "CYP2B6 SNPs are associated with methadone dose required for effective treatment of opioid addiction," *Addict Biol*, vol. 18, no. 4, pp. 709–716, Jul. 2013, doi: 10.1111/j.1369-1600.2011.00349.x.
27. B. B. Dennis, M. Bawor, L. Thabane, Z. Sohani, and Z. Samaan, "Impact of ABCB1 and CYP2B6 Genetic Polymorphisms on Methadone Metabolism, Dose and Treatment Response in Patients with Opioid Addiction: A Systematic Review and Meta-Analysis," *PLoS One*, vol. 9, no. 1, p. e86114, Jan. 2014, doi: 10.1371/journal.pone.0086114.
28. F. Remérand *et al.*, "The early and delayed analgesic effects of ketamine after total hip arthroplasty: a prospective, randomized, controlled, double-blind study," *Anesth Analg*, vol. 109, no. 6, pp. 1963–1971, Dec. 2009, doi: 10.1213/ANE.0b013e3181bdc8a0.
29. Y. Li *et al.*, "CYP2B6*6 allele and age substantially reduce steady-state ketamine clearance in chronic pain patients: impact on adverse effects," *Br J Clin Pharmacol*, vol.80, no. 2, pp. 276–284, Aug. 2015, doi: 10.1111/bcp.12614.
30. Q. Yan *et al.*, "Impact of CYP3A4*1G Polymorphism on Fentanyl Analgesia Assessed by Analgesia Nociception Index in Chinese Patients Undergoing Hysteroscopy," *Chin Med J (Engl)*, vol. 131, no. 22, pp. 2693–2698, Nov. 2018, doi: 10.4103/0366-6999.243934.
31. C.-H. Chen *et al.*, "Genetic polymorphisms in CYP3A4 are associated with withdrawal symptoms and adverse reactions in methadone maintenance patients," *Pharmacogenomics*, vol. 12, no. 10, pp. 1397–1406, Oct. 2011, doi:10.2217/pgs.11.103.
32. J. L. Anderson *et al.*, "Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation," *Circulation*, vol. 116, no. 22, pp. 2563–2570, Nov. 2007, doi: 10.1161/CIRCULATIONAHA.107.737312.

DOI: 10.69605/ijlbpr_13.10.2024.129

33. J. Li, S. Wang, J. Barone, and B. Malone, "Warfarin Pharmacogenomics," *P T*, vol. 34, no. 8, pp. 422–427, Aug. 2009.
34. M. H. Eckman, J. Rosand, S. M. Greenberg, and B. F. Gage, "Cost-effectiveness of using pharmacogenetic information in warfarin dosing for patients with nonvalvular atrial fibrillation," *Ann Intern Med*, vol. 150, no. 2, pp. 73–83, Jan. 2009, doi: 10.7326/0003-4819-150-2-200901200-00005.
35. J. Shi *et al*., "Dabigatran etexilate activation is affected by the CES1 genetic polymorphism G143E (rs71647871) and gender," *Biochem Pharmacol*, vol. 119, pp. 76–84, Nov. 2016, doi: 10.1016/j.bcp.2016.09.003.
36. T. Ebner, K. Wagner, and W. Wienen, "Dabigatran acylglucuronide, the major human metabolite of dabigatran: in vitro formation, stability, and pharmacological activity,"*Drug Metab Dispos*, vol. 38, no. 9, pp. 1567–1575, Sep. 2010, doi: 10.1124/dmd.110.033696.
37. M. Bernier *et al.*, "Major bleeding events in octagenarians associated with drug interactions between dabigatran and P-gp inhibitors," *J Geriatr Cardiol*, vol. 16, no. 11, pp. 806–811, Nov. 2019, doi: 10.11909/j.issn.1671-5411.2019.11.002.
38. X. He *et al.*, "Evidence for oxazepam as an in vivo probe of UGT2B15: oxazepam clearance is reduced by UGT2B15 D85Y polymorphism but unaffected by UGT2B17deletion," *Br J Clin Pharmacol*, vol. 68, no. 5, pp. 721–730, Nov. 2009, doi: 10.1111/j.1365-2125.2009.03519.x.
39. D. Kubitza, M. Becka, G. Wensing, B. Voith, and M. Zuehlsdorf, "Safety, pharmacodynamics, and pharmacokinetics of BAY 59-7939--an oral, direct Factor Xa inhibitor--after multiple dosing in healthy male subjects," *Eur J Clin Pharmacol*, vol. 61, no. 12, pp. 873–880, Dec. 2005, doi: 10.1007/s00228-005-0043-5.
40. C. T. O'connor, T. J. Kiernan, and B. P. Yan, "The genetic basis of antiplatelet and anticoagulant therapy: A pharmacogenetic review of newer antiplatelets (clopidogrel, prasugrel and ticagrelor) and anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban)," *Expert Opin Drug Metab Toxicol*, vol. 13, no. 7, pp. 725–739, Jul. 2017, doi: 10.1080/17425255.2017.1338274.
41. D. Sychev *et al.*, "Effect of CYP3A4, CYP3A5, ABCB1 Gene Polymorphisms on Rivaroxaban Pharmacokinetics in Patients Undergoing Total Hip and Knee Replacement Surgery," *High Blood Press Cardiovasc Prev*, vol. 26, no. 5, pp. 413–420, Oct. 2019, doi: 10.1007/s40292-019-00342-4.
42. A. Brings *et al.*, "Perpetrator effects of ciclosporin (P-glycoprotein inhibitor) and its combination with fluconazole (CYP3A inhibitor) on the pharmacokinetics of rivaroxaban in healthy volunteers," *Br J Clin Pharmacol*, vol. 85, no. 7, pp. 1528–1537,Jul. 2019, doi: 10.1111/bcp.13934.
43. J. Raymond *et al.*, "Pharmacogenetics of Direct Oral Anticoagulants: A Systematic Review," *Journal of Personalized Medicine*, vol. 11, no. 1, Art. no. 1, Jan. 2021, doi:10.3390/jpm11010037.
44. S. Ueshima *et al.*, "Impact of ABCB1, ABCG2, and CYP3A5 polymorphisms on plasma trough concentrations of apixaban in Japanese patients with atrial fibrillation," *Pharmacogenet Genomics*, vol. 27, no. 9, pp. 329–336, Sep. 2017, doi: 10.1097/FPC.0000000000000294.
45. S. H. Kanuri and R. P. Kreutz, "Pharmacogenomics of Novel Direct Oral Anticoagulants: Newly Identified Genes and Genetic Variants," *J Pers Med*, vol. 9, no. 1, p. 7, Jan. 2019, doi: 10.3390/jpm9010007.
46. R. B. Raftogianis, T. C. Wood, D. M. Otterness, J. A. Van Loon, and R. M. Weinshilboum, "Phenol sulfotransferase pharmacogenetics in humans: association of common SULT1A1 alleles with TS PST phenotype," *Biochem Biophys Res Commun*, vol. 239, no. 1, pp. 298–304, Oct. 1997, doi: 10.1006/bbrc.1997.7466.
47. A. Witten *et al.*, "Targeted resequencing of a locus for heparin-induced thrombocytopenia on chromosome 5 identified in a genome-wide association study," *J Mol Med (Berl)*, vol. 96, no. 8, pp. 765–775, Aug. 2018, doi: 10.1007/s00109-018-1661-6.
48. J. H. Karnes *et al.*, "A genome-wide association study of heparin-induced thrombocytopenia using an electronic medical record," *Thromb Haemost*, vol. 113, no. 4, pp. 772–781, Apr. 2015, doi: 10.1160/TH14-08-0670.
49. J. Rollin *et al.*, "Polymorphisms of protein tyrosine phosphatase CD148 influence FcγRIIA-dependent platelet activation and the risk of heparin-induced thrombocytopenia," *Blood*, vol. 120, no. 6, pp. 1309–1316, Aug. 2012, doi:10.1182/blood-2012-04-424044.
50. J. H. Karnes, "Pharmacogenetics to prevent heparin-induced thrombocytopenia: what do we know?," *Pharmacogenomics*, vol. 19, no. 18, pp. 1413–1422, Dec. 2018, doi: 10.2217/pgs-2018-0147.
51. J. C. Plaza-Plaza *et al.*, "Pharmacogenetic polymorphisms contributing to toxicity induced by methotrexate in the southern Spanish population with rheumatoid arthritis," *OMICS*, vol. 16, no. 11, pp. 589–595, Nov. 2012, doi: 10.1089/omi.2011.0142.
52. H. Hayashi *et al.*, "A single nucleotide polymorphism of reduced folate carrier 1 predicts methotrexate efficacy in Japanese patients with rheumatoid arthritis," *Drug Metab Pharmacokinet*, vol. 28, no. 2, pp. 164–168, 2013, doi: 10.2133/dmpk.dmpk-12- nt-038.
53. T. Kato, A. Hamada, S. Mori, and H. Saito, "Genetic polymorphisms in metabolic and cellular transport pathway of methotrexate impact clinical outcome of methotrexate monotherapy in Japanese patients with rheumatoid arthritis," *Drug Metab Pharmacokinet*, vol. 27, no. 2, pp. 192–199, 2012, doi: 10.2133/dmpk.dmpk-11-rg-066.
54. S. A. Owen, S. L. Hider, P. Martin, I. N. Bruce, A. Barton, and W. Thomson, "Genetic polymorphisms in key methotrexate pathway genes are associated with response to treatment in rheumatoid arthritis patients," *Pharmacogenomics J*, vol. 13, no. 3, pp. 227–234, Jun. 2013, doi: 10.1038/tpj.2012.7.
55. B. N. Cronstein, "Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis," *Pharmacol Rev*, vol. 57, no. 2, pp. 163–172, Jun. 2005, doi: 10.1124/pr.57.2.3.
56. A. Chango *et al.*, "The effect of 677C-->T and 1298A-->C mutations on plasma homocysteine and 5,10-methylenetetrahydrofolate reductase activity in healthy subjects," *Br J Nutr*, vol. 83, no. 6, pp. 593–596, Jun. 2000, doi: 10.1017/s0007114500000751.
57. "MTHFR gene polymorphisms and outcome of methotrexate treatment in patients with rheumatoid arthritis: analysis of key polymorphisms and meta-

DOI: 10.69605/ijlbpr_13.10.2024.129

analysis of C677T and A1298C polymorphisms - PubMed." Accessed: Oct. 03, 2024. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/21931346/

58. F. Behrens, M. Koehm, and H. Burkhardt, "Update 2011: leflunomide in rheumatoid arthritis - strengths and weaknesses," *Curr Opin Rheumatol*, vol. 23, no. 3, pp. 282–287, May 2011, doi: 10.1097/BOR.0b013e328344fddb.
59. A. Pawlik, M. Herczynska, M. Kurzawski, K. Safranow, V. Dziedziejko, and M. Drozdzik, "The effect of exon (19C>A) dihydroorotate dehydrogenase gene polymorphism on rheumatoid arthritis treatment with leflunomide," *Pharmacogenomics*, vol. 10, no. 2, pp. 303–309, Feb. 2009, doi: 10.2217/14622416.10.2.303.
60. P. B. Grabar, B. Rozman, D. Logar, S. Praprotnik, and V. Dolzan, "Dihydroorotate dehydrogenase polymorphism influences the toxicity of leflunomide treatment in patients with rheumatoid arthritis," *Ann Rheum Dis*, vol. 68, no. 8, pp. 1367–1368, Aug. 2009, doi: 10.1136/ard.2008.099093.
61. C. O'Doherty *et al.*, "Association of DHODH haplotype variants and response to leflunomide treatment in rheumatoid arthritis," *Pharmacogenomics*, vol. 13, no. 12, pp. 1427–1434, Sep. 2012, doi: 10.2217/pgs.12.118.
62. P. Bohanec Grabar, B. Rozman, M. Tomsic, D. Suput, D. Logar, and V. Dolzan, "Genetic polymorphism of CYP1A2 and the toxicity of leflunomide treatment in rheumatoid arthritis patients," *Eur J Clin Pharmacol*, vol. 64, no. 9, pp. 871–876, Sep. 2008, doi: 10.1007/s00228-008-0498-2.
63. P. Gadangi *et al.*, "The anti-inflammatory mechanism of sulfasalazine is related to adenosine release at inflamed sites," *J Immunol*, vol. 156, no. 5, pp. 1937–1941, Mar.1996.
64. E. Tanaka *et al.*, "Adverse effects of sulfasalazine in patients with rheumatoid arthritis are associated with diplotype configuration at the N-acetyltransferase 2 gene," *J Rheumatol*, vol. 29, no. 12, pp. 2492–2499, Dec. 2002.
65. "Mechanisms of resistance of malaria parasites to antifolates - PubMed." Accessed: Oct. 03, 2024. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/15734729/ M. Kurzawski, A. Pawlik, K. Safranow, M. Herczynska, and M. Drozdzik, "677C>T and 1298A>C MTHFR polymorphisms affect methotrexate treatment outcome in rheumatoid arthritis," *Pharmacogenomics*, vol. 8, no. 11, pp. 1551–1559, Nov. 2007, doi: 10.2217/14622416.8.11.1551.
66. M. L. Hetland *et al.*, "Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: results from eight years of surveillance of clinical practice in the nationwide Danish DANBIO registry," *Arthritis Rheum*, vol. 62, no. 1, pp. 22–32, Jan. 2010, doi: 10.1002/art.27227.
67. C. Liu *et al.*, "Genome-wide association scan identifies candidate polymorphisms associated with differential response to anti-TNF treatment in rheumatoid arthritis," *Mol Med*, vol. 14, no. 9–10, pp. 575–581, 2008, doi: 10.2119/2008-00056.Liu.
68. S. B. Krintel *et al.*, "Investigation of single nucleotide polymorphisms and biological pathways associated with response to TNFα inhibitors in patients with rheumatoid arthritis," *Pharmacogenet Genomics*, vol. 22, no. 8, pp. 577–589, Aug. 2012, doi: 10.1097/FPC.0b013e3283544043.
69. M. Umićević Mirkov *et al.*, "Genome-wide association analysis of anti-TNF drug response in patients with rheumatoid arthritis," *Ann Rheum Dis*, vol. 72, no. 8, pp. 1375–1381, Aug. 2013, doi: 10.1136/annrheumdis-2012-202405.
70. C. Bretlau, M. K. Sørensen, A.-L. Z. Vedersoe, L. S. Rasmussen, and M. R. Gätke, "Response to succinylcholine in patients carrying the K-variant of the
71. butyrylcholinesterase gene," *Anesth Analg*, vol. 116, no. 3, pp. 596–601, Mar. 2013, doi: 10.1213/ANE.0b013e318280a3f3.
72. M. C. McGuire *et al.*, "Identification of the structural mutation responsible for the dibucaine-resistant (atypical) variant form of human serum cholinesterase," *Proc NatlAcad Sci U S A*, vol. 86, no. 3, pp. 953–957, Feb. 1989, doi: 10.1073/pnas.86.3.953.