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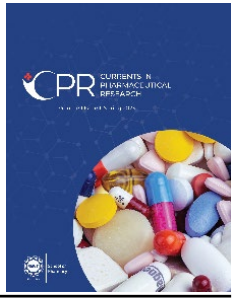

Title:	**Balancing Releif and Pain: Effects of COX-2 Inhibitor Valdecoxib**
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Balancing Relief and Pain: Effects of COX-2 Inhibitor Valdecoxib

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ABSTRACT

Valdecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, was initially acclaimed for its gastrointestinal safety and effectiveness in managing chronic inflammatory conditions and pain. It reduced gastrointestinal complications compared to other anti-inflammatory drugs, benefiting patients with complex medication regimens. The injectable form, parecoxib, was seen as promising for acute post-surgery pain management. However, clinical trials in high-risk cardiovascular patients, particularly those undergoing coronary artery bypass grafting, revealed increased risks when using higher doses of parecoxib. These findings led to the re-evaluation of valdecoxib's safety profile and its subsequent market withdrawal due to cardiovascular concerns and reports of serious skin reactions. Despite its withdrawal, valdecoxib has garnered interest for repurposing in other conditions. Its pharmacodynamic and pharmacokinetic properties suggest potential in qualifying palmitate-induced insulin resistance in type 2 diabetes and inhibiting matrix metalloproteinases for wound healing. Its efficacy against SARS-CoV-2 highlights drug repurposing strategies for health crises like COVID-19. Valdecoxibs established success in arthritis, dysmenorrhea, and postoperative pain, along with its potential in treating glaucoma, underscores the value of repurposing existing drugs for new therapeutic purposes. In conclusion, valdecoxib exemplifies the balance between drug safety, clinical utility, and innovative repurposing. The aim of this study is to fully harness drug potential in medical science through a concerted effort made by the scientific community, regulatory bodies, and industry stakeholders to navigate the technological and regulatory hurdles.

Keywords: Cyclooxygenase-2 (COX-2), drug, gastrointestinal, parecoxib, recall, regulatory framework, safety, valdecoxib

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1. INTRODUCTION

Product recall is a process that involves the withdrawal of a drug from the market due to the defect or danger it poses to consumers or due to a violation of federal law. On the contrary, market withdrawal is a process that involves the removal of a drug from the market to correct a minor issue that does not pose danger to consumers and is not technically subject to legal action by the US Food and Drug Administration (FDA). The difference between these two processes lies in the risk of harm that the particular drug causes to the consumers. A product recall is initiated when there is a significant risk of harm posed by the drug, while a market withdrawal is carried out when there is no significant risk of harm posed by the particular drug. Various reasons can lead to drug recalls, such as concerns related to safety, mislabelling, contamination, or deviations in strength or potency. Drug recalls can be initiated voluntarily by the supplier or the manufacturer, at the request of the FDA, or as a legally mandated order from the FDA [1–2].

Valdecoxib (BEXTRA®) is a nonsteroidal anti-inflammatory drug (NSAID) approved by the FDA on November 20, 2001 for the treatment of conditions such as dysmenorrhea, rheumatoid arthritis, and most commonly, osteoarthritis [3, 4]. It was manufactured and marketed by G. D. Searle, a subsidiary of Pfizer in 2005 under the brand name BEXTRA®. In 2005, Pfizer voluntarily withdrew valdecoxib from the market due to the concerns of an increase in the risk of stroke and heart attack [5]. A study published in The New England Journal of Medicine found the drug to be associated with an increased risk of cardiovascular events [6]. The recall of valdecoxib was an important event in the history of drug recalls. It highlighted the importance of monitoring drug safety after it being approved by regulatory agencies, such as FDA. It also indicated the need for physicians and patients to be aware of the potential risks associated with drugs and to weigh these risks against their potential benefits when making treatment decisions.

1.1. Pharmacology of Valdecoxib

The chemical name of valdecoxib is 4-(5-methyl-3-phenyl-4-isoxazolyl) benzene sulphonamide. It is a diaryl-substituted isoxazole with a molecular weight of 314.36 g/mol. Its chemical formula is C16H14N2O3S. The skeletal structure of valdecoxib is shown in Fig. 1 [7].

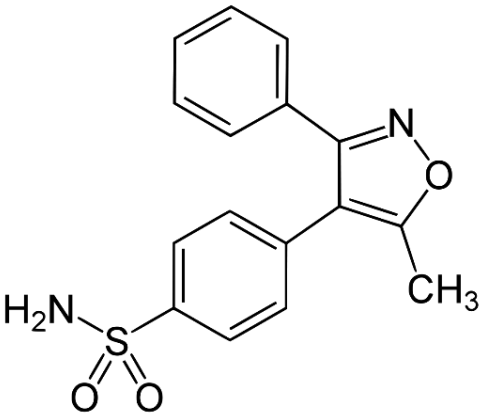

Figure 1. Chemical Structure of Valdecoxib (Adopted from Gupta V et al.)

Valdecoxib belongs to the nonsteroidal anti-inflammatory drugs (NSAIDs) class and possesses anti-inflammatory, analgesic, and antipyretic properties. Its mechanism of action involves the inhibition of prostaglandin synthesis which contributes to inflammation and pain. Specifically, valdecoxib selectively targets cyclooxygenase-2 (COX-2), an enzyme-producing prostaglandins. It is important to note that at normal therapeutic plasma concentrations in humans, this drug has been known to have no action on COX-1. This fact distinguishes it from other NSAIDs. COX-2 inhibitors, unlike other NSAIDs, do not affect COX-1 enzymes that produce prostaglandins for stomach lining protection and blood clotting. COX-2 inhibitors are specifically used for treating arthritis and short-term pain caused by inflammation. A study published in BMC Anaesthesiology found that valdecoxib was quite effective in treating acute postoperative pain [3].

1.2. Pharmacokinetics of Valdecoxib

Valdecoxib attains its peak blood concentration approximately three (03) hours after oral administration as BEXTRA. When taken orally, about 83% of the drug is absorbed into the bloodstream, compared to intravenous infusion. The relationship between dose and exposure was established by administering single doses of the drug ranging from 1 mg to 400 mg, demonstrating dose proportionality. However, when taken multiple times a day for up to 14 days, exposure increases in a more than proportional manner at doses exceeding 10 mg BID (two times a day), indicated by the area under the concentration-time curve (AUC) value in Table 1. By the 4th

day of administration, steady-state plasma concentrations of the drug are achieved [8]. The pharmacokinetic parameters set by the published work involving healthy male subjects (n=8, 20-42 years) are displayed in Table 1 [4].

Table 1. Descriptive of Steady-State Pharmacokinetic Parameters of Valdecoxib in Healthy Male Subjects

Pharmacokinetics Parameters	Mean (SD)
$AUC_{(0\text{-}24hr)}$ (hr.ng/mL)	1479.0 (291.9)
C_{max} (ng/mL)	161.1 (48.1)
T_{max} (hr.)	2.25 (0.71)
C_{min} (ng/mL)	21.9 (7.68)
Elimination Half-life (hr.)	8.11 (1.32)

Note. * Steady State Pharmacokinetic Characteristics Following 14-Day OD Valdecoxib 10 mg. yr: year, hr: hour, ng: nanograms, ml: milliliter (Adopted from FDA Database)

There are currently 351 drugs that are known to interact with valdecoxib. Of these, 06 are minor, 287 are moderate, and 58 are major interactions. Valdecoxib may increase the risk of bleeding when taken with aspirin, fish oil, or pregabalin. Moreover, it should not be taken concurrently with other NSAIDs such as celecoxib (as they belong to the same drug class) or clopidogrel, since their concurrent administration can heighten the risk of side effects. Additionally, valdecoxib may reduce the effectiveness of folic acid, hydrochlorothiazide, furosemide, esomeprazole, pantoprazole, levothyroxine, and vitamin B12 when taken concomitantly. Combining valdecoxib with lisinopril, atenolol, metoprolol, losartan, or prednisone may increase the risk of side effects [9].

Individuals with sulphonamide allergy are not recommended to take valdecoxib. Its use is also contraindicated in patients with urticaria or allergic-type reactions (including asthma) after the use of NSAIDs or the intake of aspirin. In such patients, severe but fatal anaphylactic-like reactions, although rare, are possible due to the use of NSAIDs. Hence, valdecoxib is not recommended for the alleviation of pain after a coronary artery bypass graft (CABG) surgery [8].

1.3. Safety Profile of Valdecoxib

The impact of valdecoxib on renal safety has raised concerns due to the role of the COX-2 enzyme in renal vasodilation, facilitated by prostacyclin production in endothelial cells. The renal safety profile of valdecoxib has been extensively investigated in patients with rheumatoid arthritis and osteoarthritis. In combined studies, the occurrence of common renal side effects associated with COX-2 inhibition, such as albuminuria, peripheral edema, and hypertension were more frequent as compared to placebo but did not show a statistically significant difference when compared to conventional NSAIDs [10, 6]. Studies in patients with severe renal dysfunction and end-stage renal dysfunction undergoing hemodialysis revealed a decrease of 23% in mean plasma clearance as compared to a group of healthy control individuals. However, this reduction was not considered clinically significant enough to necessitate a dosage adjustment in cases of renal insufficiency. Nevertheless, it is strongly advised against the use of valdecoxib in individuals with advanced renal diseases. Most renal effects associated with this drug are dose-dependent and linked to the occurrence of edema and an increase in blood pressure. Consequently, when administering valdecoxib to individuals reliant on the renin-angiotensin system hemodynamics (such as those with cirrhosis or congestive heart disease), careful monitoring of the renal function is recommended [11].

One of the most significant side effects associated with valdecoxib is an increase in the risk of cardiovascular and thromboembolic events, such as myocardial infarction, pulmonary embolism, and stroke. According to a study, patients taking this drug were shown to have a higher risk of cardiovascular events in comparison to those taking a placebo. Furthermore, they were shown to have a relative risk of 2.26 for confirmed thrombotic events (including myocardial infarction, stroke, and death) as compared to those taking a placebo [12]. Another study reported that valdecoxib is associated with an increase in the risk of serious skin reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, as well as the development of erythema multiforme [12]. The study analyzed data from the FDAs Adverse Event Reporting System (AERS) and found that the drug was associated with a higher proportion of serious skin reactions, as compared to other NSAIDs. Other side effects associated with this drug

included gastrointestinal bleeding and liver toxicity. These side effects are summarized in Table 2 below.

Table 2. Common Side Effects of Valdecoxib

Systems	Side Effects
Cardiovascular	(< 2%) worsened hypertension, aneurysms, angina, arrhythmias, cardiomyopathies, heart failure, coronary artery disorder, murmurs, and hypotension
Nervous system	Dizziness, Migraines, and headaches
Dermatological	Rashes
Endocrine	Hyperglycemia
Gastrointestinal	Abdominal pain, diarrhea, dyspepsia, flatulence, nausea
Hepatic	Increased liver enzymes
Metabolic	Edema
Musculoskeletal	Back pain/lumbago

1.4. Counterarguments and Repurposing of Valdecoxib

Drug repurposing, also known as drug repositioning, attempts to find alternate therapeutic benefits of many drugs. The advantage of this repurposing is that it is not only cost effective but also saves time. Rather than developing new drugs, these drugs have been approved already, have passed all the phases of clinical trials, and have been studied extensively for their efficacy and safety profile. Hence, they carry the potential to provide therapeutic benefits in case of refractory conditions and rare diseases that cannot be treated by conventional drugs [13]. One such example includes aspirin, a commonly used analgesic also used for its antiplatelet action in cardiac and other diseases. It has been discovered recently to block pro-inflammatory cytokine secretion from cancer cells and also helps in the clearance of cancer cell debris via the activation of macrophages [14, 15]. Similarly, another NSAID celecoxib was used originally in the treatment of osteoarthritis. It has been approved for reducing the risk of colon cancer by reducing the risk of the formation of more polyps. Moreover, it also reduces the risk of colorectal cancer in the general population [16].

In the realm of rheumatology, valdecoxib distinguished itself as an efficacious medication, particularly for its lower propensity to cause gastrointestinal issues relative to its COX-2 inhibitor counterparts. This

characteristic proved especially beneficial for rheumatology patients, who frequently are prescribed a regimen of multiple medications, some of which may have gastrointestinal side effects. The introduction of an injectable form of the drug further enhanced its value, offering a practical solution for the management of disease flare-ups in rheumatology patients' post-surgery.

However, the primary advantage of valdecoxib, encapsulated in its parenteral form known as parecoxib, prompted its evaluation in a patient demographic characterized by a heightened risk of cardiovascular events. These trials focused on patients who had recently undergone coronary bypass graft surgery, a procedure intrinsically associated with an increased risk of thrombotic complications. In these trials, parecoxib was administered in doses significantly higher than those traditionally employed in rheumatologic care or explored within rheumatology-focused research, leading to a pronounced inhibition of COX-2 pathways [17].

Despite these cardiovascular concerns mirrored in the case of celecoxib, the latter remains extensively utilized in clinical practice. The relatively lower cardiovascular risk associated with its usage might be attributed to the specific contexts of its administration and application [18].

The clinical trials involving valdecoxib underscored significant safety concerns, particularly emphasizing the elevated risk of thrombosis in patients with cardiovascular conditions. These findings spurred debate over the selective withdrawal of COX-2 inhibitors, including valdecoxib and rofecoxib, fuelled by the reports of potentially fatal skin reactions and cardiovascular embolic events linked to valdecoxib, though the accuracy of these reports has since been contested.

In light of these safety concerns, particularly the risk of cardiovascular complications, selective COX-2 inhibitors such as valdecoxib were withdrawn from the market. Nevertheless, there is a burgeoning interest in repurposing these drugs for a variety of conditions, ranging from cancer to epilepsy, psychiatric disorders, obesity, and Alzheimers disease. This paradigm shift underscores a holistic strategy aimed at harnessing their therapeutic potential beyond their initial indications, advocating for a unified and science-based approach to drug repurposing. This perspective not only reconciles with past controversies but also forecasts a promising horizon for these compounds across diverse medical applications [19].

The repurposing of valdecoxib, a selective COX-2 inhibitor initially approved for pain and inflammation, unveils a spectrum of potential therapeutic applications beyond its original designation. The current research highlights its potential to address various diseases including cancer, epilepsy, psychiatric disorders, obesity, and Alzheimer's disease, thus demonstrating its expansive therapeutic implications [19]. This vast potential emphasizes the importance of re-evaluating well-established drugs for novel therapeutic purposes, as well as leveraging their known pharmacodynamics, pharmacokinetics, and safety profiles to accelerate the drug development process.

Specifically, the structural properties of this drug have been investigated for their potential against matrix metalloproteinases (MMPs), indicating a promising path for enhancing wound healing capabilities. This research points to the viability of repurposing existing drugs for new therapeutic targets, thus not only expanding their application but also enhancing patient care outcomes in areas such as delayed wound healing [20].

Furthermore, the ongoing COVID-19 pandemic has necessitated swift drug repurposing strategies. Valdecoxib has been identified among compounds with potential efficacy against SARS-CoV-2, showcasing the adaptability of drug repurposing efforts in tackling the emergent global health crises [21]. This approach not only highlights the flexibility of modern pharmacology in addressing unforeseen challenges but also emphasizes the importance of comprehensive drug databases and computational methods in identifying promising repurposing candidates.

Despite the promising outlook of repurposing valdecoxib, transitioning from concept to clinical applications entails navigating technological and regulatory hurdles. Successful drug repositioning initiatives require a collaborative approach, incorporating insights from various scientific disciplines and simplifying regulatory processes to ensure the seamless integration of repurposed drugs into clinical practice [22].

Research indicates that valdecoxib significantly enhances glucose uptake in skeletal muscle cells and also enhances the signaling of insulin, offering a potential pharmacotherapeutic option for managing insulin resistance and type 2 diabetes [23]. Its documented efficacy in pain

management for conditions such as osteoarthritis, rheumatoid arthritis, primary dysmenorrhea, and postoperative pain, coupled with a lower incidence of gastrointestinal complications, highlights its potential for broader pain management applications [24].

The repurposing of old drugs for new therapeutic uses in fields like oncology is gaining momentum. Advances have revealed many old drugs to show activity at novel antioncogenic pharmacological targets, suggesting their potential beyond their initial indications [25].

Furthermore, valdecoxib has been shown to prevent endoplasmic reticulum stress-induced cell death in experimental glaucoma by blocking the PERK-ATF4-CHOP pathway, indicating its therapeutic potential in neurodegenerative diseases, especially in managing retinal ischemia-reperfusion injury [26].

Addressing technological and regulatory challenges in drug repurposing is essential to fully realize the potential of valdecoxibs repurposing. Innovative approaches are recommended to efficiently navigate these barriers [27].

2. CONCLUSION

To conclude, the repurposing of valdecoxib represents the broader potential of re-evaluating existing pharmaceuticals for new therapeutic uses. This strategy offers a cost-effective pathway to drug development and holds the promise of meeting unmet medical needs across various health conditions. As the field progresses, its crucial to support these efforts with solid scientific evidence and adaptable regulatory frameworks to navigate the dynamic landscape of drug repurposing.

CONFLICT OF INTEREST

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVALIABILITY STATEMENT

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