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Potential Drug-Drug Interactions Associated With Nsaids in a Tertiary Care Hospital

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ABSTRACT
NSAIDsare a class of drugs that are widely used in management of pain and inflammation in many conditions and are also easily available as over the counter of drugs which makes them more vulnerable to potential drug-drug interactions. The main aim of the study is to analyse the potential drug-drug interactions of NSAIDs. A prospective observational study was conducted in the Orthopedic and Surgery department of a 450 bedded tertiary care hospital for a period of 6 months. Adult patients of either sex admitted to these departments receiving NSAIDs where included. Patients below the age of 18 years,pregnant and lactating mothers receiving NSAIDs patients admitted to other departments receiving NSAIDs were excluded from the study. Out of 274 interactions 20 were major, 184 were moderate, and 70 were minor interactions. Classification of interactions based on their risk rating by Lexicomp 78 interactions were in category C, 14 in category D, 6 each in category X and category B. NSAIDs were found to interact mostly with other NSAIDs (95.00%). PPIs were the most commonly co-prescribed class of drugs along with NSAIDs considering their GI side effects.
Keywords: Analgesic, Anti-inflammatory, LEXICOMP, NSAID, proton pump inhibitors, drug interaction.

I. INTRODUCTION

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs), including both traditional and non-selective NSAIDs and the selective cyclooxygenase (COX)-2 inhibitors, are widely used for their anti-inflammatory and analgesic effects. They are a necessary choice in pain management because of the integrated role of the COX pathway in then generation of inflammation and in the biochemical recognition of pain. NSAIDs are used for a variety of conditions including pain, rheumatoid arthritis, and musculoskeletal disorders. The beneficial effects of NSAIDs in reducing or relieving pain are well established, and other benefits such as reducing inflammation and anticancer effects are also documented. The undesirable side effects of NSAIDs include ulcers, internal, bleeding, kidney failure, and increased risk of heart attack and stroke.

CLASSIFICATION
1. Nonselective COX Inhibitors (Traditional NSAIDs)
1. Salicylates: Aspirin
2. Propionic acid derivatives: Ibuprofen, Naproxen, Flubiprofen, Ketoprofen.
3. Fenamates: Mephenamic acid
4. Enolic acid derivatives: Piroxicam, Tenoxicam,Lornoxicam
5. Acetic acid derivatives: Ketorolac, Indomethacin, Nabumetone
6. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone

2. Preferential COX-2 inhibitors
Nimesulide, diclofenac,Aceclofenac, Meloxicam, Etodolac
3. Selective COX-2 inhibitors
Celecoxib, Etoricoxib,Parecoxib

4. Analgesic-antipyretic with poor anti-inflammatory action
1. Para-aminophenol derivative: Paracetamol
2. Pyrazolone derivatives: Metamizol, Propyphenazone
3. Benzoxazocine derivative: Nefopam.

MECHANISM OF ACTION
The cyclooxygenase (COX) enzyme is inhibited by NSAIDs, which is their primary mode of action. Arachidonic acid must be converted by cyclooxygenase in order to produce prostacyclins, prostaglandins, and thromboxanes. The absence of

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these eicosanoids is thought to be the cause of NSAIDs' therapeutic effects. In particular, prostaglandins produce vasodilation, raise the hypothalamic temperature set-point, and contribute to anti-nociception, whereas thromboxanes aid in platelet adhesion.

COX-1 and COX-2 are the two cyclooxygenase isoenzymes. The body constitutively expresses COX-1, which contributes to renal function, platelet aggregation, and the preservation of the lining of the gastrointestinal tract. COX-2 is inducibly expressed during an inflammatory reaction rather than constitutively expressed in the body. The majority of NSAIDs inhibit both COX-1 and COX-2 and are nonselective. However, because they only target COX-2, COX-2 selective NSAIDs (such celecoxib) have a different profile of side effects. Crucially, COX-2 selective NSAIDs should offer anti-inflammatory treatment without endangering the gastric mucosa because COX-2 is primarily involved in inflammation and COX-1 is the primary mediator for maintaining the integrity of the gastric mucosa.

THERAPEUTIC ACTIONS

1. ANTI-INFLAMMATORY EFFECTS

Inhibition of COX-2-mediated increased PG production at the site of injury is thought to be the primary mechanism of NSAIDs' anti-inflammatory effect. Nonetheless, there is evidence that inhibiting constitutive COX-1 also helps to reduce inflammation, particularly in its early phases. PGs are merely one type of mediator of inflammation; the synthesis of other mediators, such as LTs, PAF, cytokines, etc., is not suppressed by COX inhibition.

2. ANTIPYRETIC EFFECT

Normal body temperature is controlled by the hypothalamic centre that regulates the balance of heat generation to heat loss. When this hypothalamus "thermostat," which boosts body temperature, is disturbed, fever occurs. This thermostat is "reset" by NSAIDs. Normal body temperature in healthy humans is not affected by NSAIDs

3. ANALGESIC EFFECTS

The NSAIDs are effective against mild or moderate pain, especially that arise from inflammation or tissue damage. Two sites of action have been identified. Peripherally, NSAIDs decrease production of prostaglandins that sensitise nociceptors to inflammatory mediators such as bradykinin and they are effective in arthritis, bursitis, pain of muscular and vascular origin, toothache, dysmenorrhea, the pain of postpartum states and pain of cancer metastasis in body. All conditions are associated with increased local prostaglandin synthesis probably as a result of COX-2 induction. Alone, or in combination with opiods by as much as one third. In addition to these peripheral effects, there is a second, less well characterised central action, possibly in the spinal cord. Peripheral inflammatory lesions increase COX-2 expression and prostaglandin, release within the cord, facilitating transmission from afferent pain fibres to relieve neurons in the dorsal horn.

4. ANTIPLATELET AGGREGATORY EFFECTS

NSAIDs inhibit the synthesis of both pro-aggregatory(TXA_2) and anti-aggregatory (PGI_2) prostanoids, but effect on platelet TXA_2 (COX-1 generated) predominates. The therapeutic doses of NSAIDs inhibit platelet aggregation: bleeding time is prolonged. Aspirin is highly active; acetylates platelet COX irreversibly in the portal circulation before it is de-acetylated by first pass metabolism in liver. Small doses are therefore able to expert anti-thrombotic effect for several days. Risk of surgical and anti-coagulant associated bleeding is enhanced.

UNWANTED EFFECTS

The gastrointestinal mucosa, cardiovascular system, hepatic system, renal system, and haematologic system are all known to be negatively impacted by NSAIDs.

Gastric adverse effects

The inhibition of COX-1, which stops the production of prostaglandins that shield the gastric mucosa, is probably the cause of the negative effects in the stomach. Patients with a history of peptic ulcers are more prone to sustain harm. The usage of COX-2 selective NSAIDs is a less dangerous option because it is COX-1 specific.

Renal adverse effects

The reason for the negative effects on the kidneys is that COX-1 and COX-2 promote the synthesis of prostaglandins, which are involved in renal haemodynamics. Inhibiting prostaglandin synthesis does not present a significant issue in patients with normal renal function; however, in

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patients with renal failure, prostaglandins are more important and can cause issues when lowered with NSAIDs. Elevated blood pressure, acute renal failure, fluid and electrolyte imbalances, renal papillary necrosis, and nephrotic syndrome/interstitial nephritis are among the possible complications.

Cardiovascular adverse effects

NSAID use may potentially raise the risk of cardiovascular side effects, such as atrial fibrillation, thromboembolic events, and MI. The NSAID with the biggest documented increase in adverse cardiovascular events appears to be diclofenac.

Hepatic adverse effects

There is a lower incidence of hepatic side effects, NSAID-associated hepatotoxicity (higher aminotransferase levels), and liver-related hospitalisation. Diclofenac has a higher incidence of hepatotoxic consequences than the other NSAIDs.

Hematologic adverse effects

Because nonselective NSAIDs have antiplatelet activity, haematologic side effects are likely. Usually, this antiplatelet effect is only problematic if the patient has a history of gastrointestinal ulcers, illnesses that affect platelet function (such as von Willebrand, thrombocytopenia, haemophilia, etc.), or in certain perioperative situations.

Other minor adverse effects

Anaphylactoid reactions affecting the skin and pulmonary systems, such as urticaria and aspirin-exacerbated lung disease, are among the other mild side effects.

DRUG-DRUG INTERACTIONS

A modification in the way a drug affects the body when taken alongside another drug. Both drugs' absorption may be slowed down, increased, or delayed by a drug-drug interaction. This may result in negative side effects or alter the way one or both medications work.

With a prevalence of 20–40%, drug-drug interactions (DDIs) are one of the most frequent reasons for medication errors in developed nations, especially in older patients who are receiving multiple medications. Specifically, polytherapy raises the possibility of clinically significant DDIs, which can either decrease clinical efficacy or cause adverse medication reactions, by complicating therapeutic management. The two primary categories of DDIs are pharmacokinetic and pharmacodynamic.

Antagonism and synergism.

When two chemicals interact in a way that inhibits or interferes with one another's effects, this is referred to as antagonism. On the other hand, the combination of two drugs that intensifies or amplifies their effects is referred to as synergism. Synergism produces a stronger combined effect than either chemical would have on its own, whereas antagonism reduces total effectiveness.

Pharmacodynamic interactions

When the pharmacological impact of one medication is changed by that of another in a combination regimen, this is known as a pharmacodynamic drug-drug interaction (DDI). DDIs are frequently categorised as antagonistic, additive, or synergistic.

Pharmacodynamic interaction of NSAIDs

Interactions involving platelets— It is well known that taking NSAIDs at the same time raises the risk of gastrointestinal bleeding by increasing the COX-1-mediated suppression of thromboxane production. Ibuprofen's specific and reversible binding to COX-1, which stops acetylsalicylic acid (ASA) from acetylating the serine residue at position 529 of the COX-1 protein, is one of its unique characteristics. The cardiac risk of people with coronary heart disease may rise as a result of ASA's irreversible and thus long-lasting suppression of COX-1-mediated thromboxane A2 production.

These ex vivo findings are supported by long-term clinical observations, which seem to apply to naproxen as well. As a result, those with coronary heart disease receiving ASA prophylaxis shouldn't regularly take naproxen or ibuprofen. Simultaneous use of NSAIDs and selective serotonin reuptake inhibitors (SSRIs), such citalopram, can also increase gastrointestinal bleeding. SSRIs cause further function impairment and double the risk of bleeding by blocking the transport of serotonin into the platelets. Vitamin K antagonists like warfarin and phenprocoumon can further raise the risk of bleeding via impairing platelet function through SSRIs.

Vascular system interactions: NSAIDs may lessen the ACE inhibitors' ability to control blood pressure. The primary mechanism is a

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decrease in glomerular perfusion brought on by a decrease in local prostaglandin E2 production and the reactive release of renin.

Pharmacokinetic interactions

When a drug's absorption, transport, distribution, metabolism, or excretion differs from how each drug should behave when taken separately, the result is a modification in the drug's action. These alterations are essentially adjustments to the drug's concentration.

The pharmacokinetic interactions can be divided into 3 classes:
(1) Drugs affecting the pharmacokinetics of an NSAID.
(2) An NSAID interfering with the pharmacokinetics of another NSAID
(3) NSAIDs altering the pharmacokinetics of another drug

Although concurrent use of sucralfate or antacids may slow the rate of oral NSAID absorption, this effect is usually minimal. Antacid use raises the pH of the urine, which causes the kidneys to excrete more salicylic acid that hasn't been altered and lowers the antirheumatic drug's plasma concentrations. Cimetidine, an H2-receptor blocking medicine, prevents the oxidative metabolism of numerous medications taken at the same time, including certain NSAIDs. Because probenecid prevents the kidneys from secreting drug glucuronides, NSAIDs that are mostly removed by the production of labile acyl glucuronides, like naproxen, ketoprofen, indomethacin, and carprofen, will accumulate in the plasma.Cholestyramine reduces the oral absorption of NSAIDs and many other medications taken at the same time. By disrupting the enterohepatic cycle, it may also lower the plasma concentrations of NSAIDs that are undergoing enterohepatic circulation, such as piroxicam and tenoxicam. Low plasma salicylate concentrations result from corticosteroids' stimulation of salicylic acid clearance. When an NSAID and aspirin are taken together, the plasma concentrations of several NSAIDs are considerably decreased.

The disposition kinetics of several additional medications may be considerably impacted by NSAIDs. They have the ability to block the metabolism, interfere with renal excretion, or displace other medications from their binding sites on plasma proteins. The interaction might be clinically relevant if the impacted medication has a narrow therapeutic index. The metabolism of numerous medications, including coumarin anticoagulants, oral antidiabetics, and anticonvulsants like phenytoin, is inhibited by the pyrazole NSAIDs (phenylbutazone, oxyphenbutazone, and azapropazone). Oral anticoagulants are displaced from their plasma protein binding sites by salicylates. Additionally, aspirin raises the risk of bleeding by causing stomach erosions and inhibiting platelet activity.In this study we analyze the drug-drug interaction by two tools: Lexicomp online interaction checker and Medscape multi-interaction checker. The interactions could be classified based on their severity and risk rating.

DRUG INTERACTION RISK RATING BY LEXICOMP

Risk rating	Description	Action
A	Data have not demonstrated either pharmacodynamic/pharmacokinetic interactions with specified agents	No interaction
B	Data demonstrated that specific agents may interact with each other, but there is little to no evidence	No action needed
C	Data demonstrated that specific agents may interact with each other in clinically significant manner. The benefits of concomitant use of these medication usually outweigh the risk.	Monitor therapy
D	A patient specific assessment must be conducted to determine whether the benefits outweigh the risk	Monitor regimen
X	Risks associated with the concomitant use outweigh benefits usually	Avoid combination

TABLE 1:DRUG INTERACTION RISK RATING BY LEXICOMP

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DRUG INTERACTION SEVERITY RATING BY LEXICOMP

Severity rating	Action
Major	Avoid combinations/Modify regimens
Moderate	Monitor therapy
Minor	No action needed

TABLE 2:DRUG INTERACTION SEVERITY RATING BY LEXICOMP

DRUG INTERACTION SEVERITY RATING BY MEDSCAPE

Severity rating	Action
Serious	Use alternative
Moderate	Monitor closely
Minor	No action needed

TABLE 3: DRUG INTERACTION SEVERITY RATING BY MEDSCAPE

AIM AND OBJECTIVES

1. To monitor and evaluate the prescribing pattern and potential drug- drug interactions of NSAIDs in a tertiary care hospital.
2. To evaluate prescribing pattern of NSAIDs
3. To classify drug- drug interactions associated with NSAIDs
4. To classify drug- drug interactions based on their severity using Lexicomp and Medscape.
5. To detect most commonly prescribed NSAID among the population.

METHODOLOGY

STUDY SITE

The study was conducted in the orthopaedic and surgery department of a 450 bedded tertiary care hospital.

STUDY DURATION

The study was carried out for a period of 6 months in the orthopaedic and surgery department of a tertiary care hospital.

STUDY DESIGN

The study was designed to be a prospective observational study for which the sample population was selected based on inclusion exclusion criteria. The study was conducted by collecting data from the medical records of inpatients receiving NSAIDs in orthopaedic and surgery department.

SAMPLE SIZE

A total of 100 patients were enrolled in the study.

STUDY CRITERIA

Inclusion criteria

1. Patients above 18 years
2. Patients of either gender
3. Patients admitted in orthopaedic and surgery department receiving NSAIDs.

Exclusion criteria

1. Pregnant and lactating women
2. Patients receiving NSAIDs other than in surgery and orthopaedic department

STUDY PROTOCOL

The protocol of the study was submitted to institutional Human ethics committee of hospital. The protocol was approved by the committee with the approval number.

STUDY MATERIALS

A specifically designed data entry form, interactions checkers, statistical tools for diagrammatic representations.

STATISTICAL ANALYSIS

Descriptive statistics were used to analyse the results. Percentage and averages of variables were also calculated.

PLAN OF THE STUDY

1. Phase 1: An extensive literature survey designing of customised data entry form and obtaining approval form hospital committee.
2. Phase 2: Collection of required patient details from the patient medical records.
3. Phase 3: Data analysis for prescribing trends and potential drug- drug interactions associated with NSAIDs descriptive statistical analysis for comparisons
4. Phase 4: Submission of report.

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II. RESULTS

1. GENDER
N=100

GENDER	NUMBER OF CASES	PERCENTAGE
MALE	24	24%
FEMALE	76	76%

TABLE 4: DISTRIBUTION BASED ON GENDER

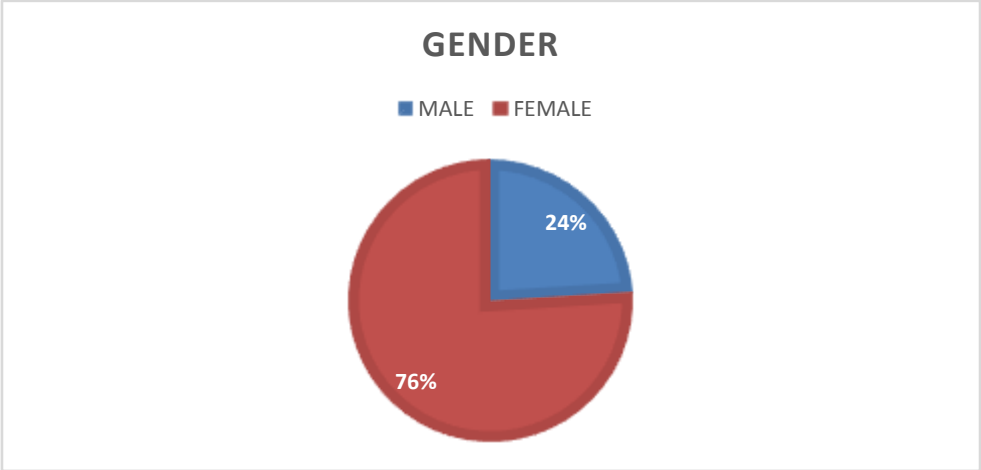

FIGURE 1: DISTRIBUTION BASED ON GENDER

2. AGE
N=100

AGE(YEARS)	NUMBER OF CASES	PERCENTAGE
18-38	27	27%
39-59	47	47%
≥60	26	26%

TABLE 5: DISTRIBUTION BASED ON AGE

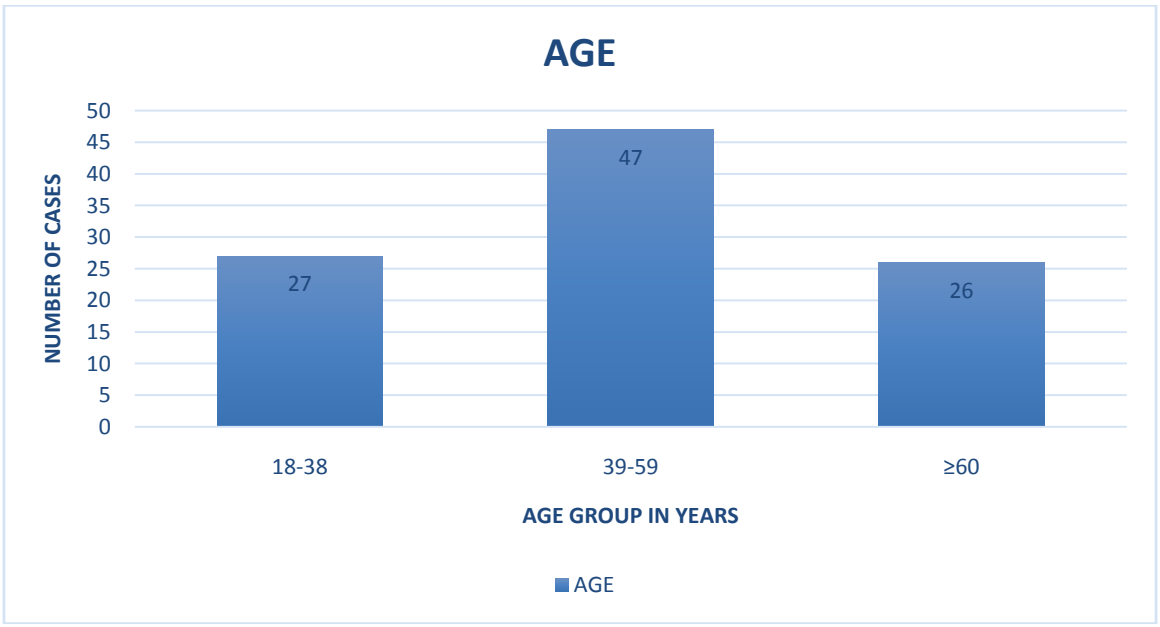

FIGURE 2: DISTRIBUTION BASED ON AGE

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3. NUMBER OF NSAIDS PRESCRIBED
N=100

NUMBER OF NSAIDS PRESCRIBED	NUMBER OF CASES	PERCENTAGE
MONO THERAPY	45	45%
DUAL THERAPY	38	38%
MULTIPLE THERAPY(≥3)	17	17%

TABLE 6: DISTRIBUTION BASED ON NUMBER OF NSAIDS PRESCRIBED

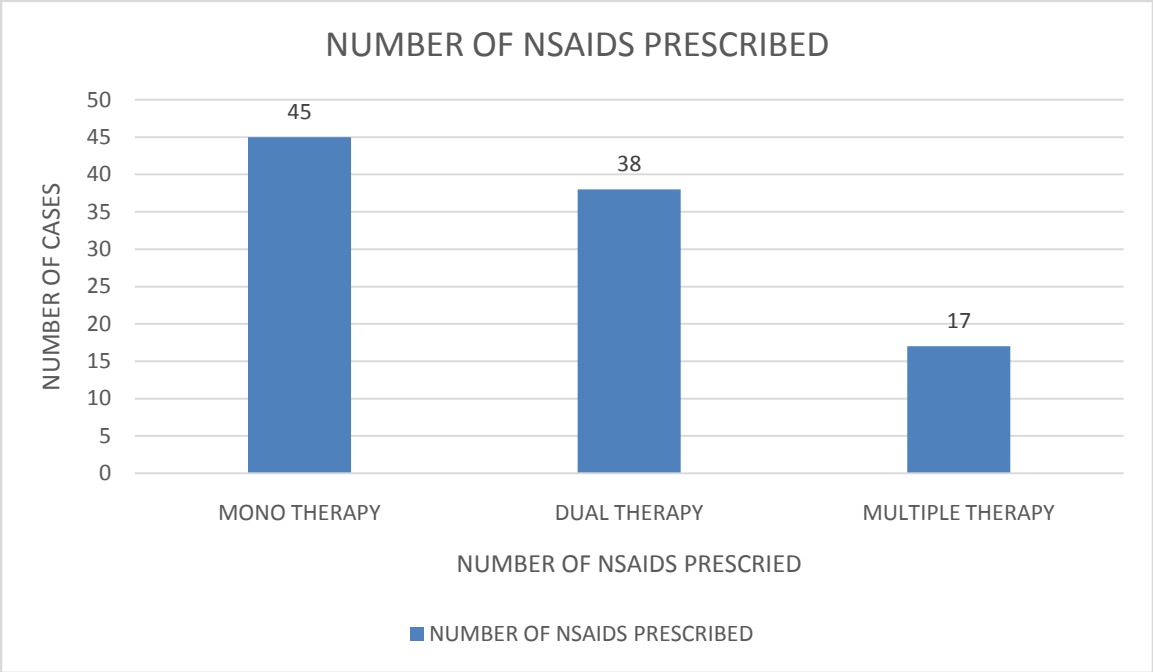

FIGURE 3: DISTRIBUTION BASED ON NUMBER OF NSAIDS PRESCRIBED

4. TYPE OF NSAIDS PRESCRIBED
N=177

NAME OF NSAID	NUMBER OF CASES	PERCENTAGE
LORNOXICAM	52	29.37%
PARACETAMOL	38	21.46%
DICLOFENAC	35	19.77%
ETORICOXIB	24	13.55%
ACECLOFENAC	10	5.64%
IBUPROFEN	7	3.95%
INDOMETHACIN	7	3.95%
PIROXICAM	3	1.69%
MEFENAMIC ACID	1	0.56%

TABLE 7: DISTRIBUTION BASED ON TYPE OF NSAIDS PRESCRIBED

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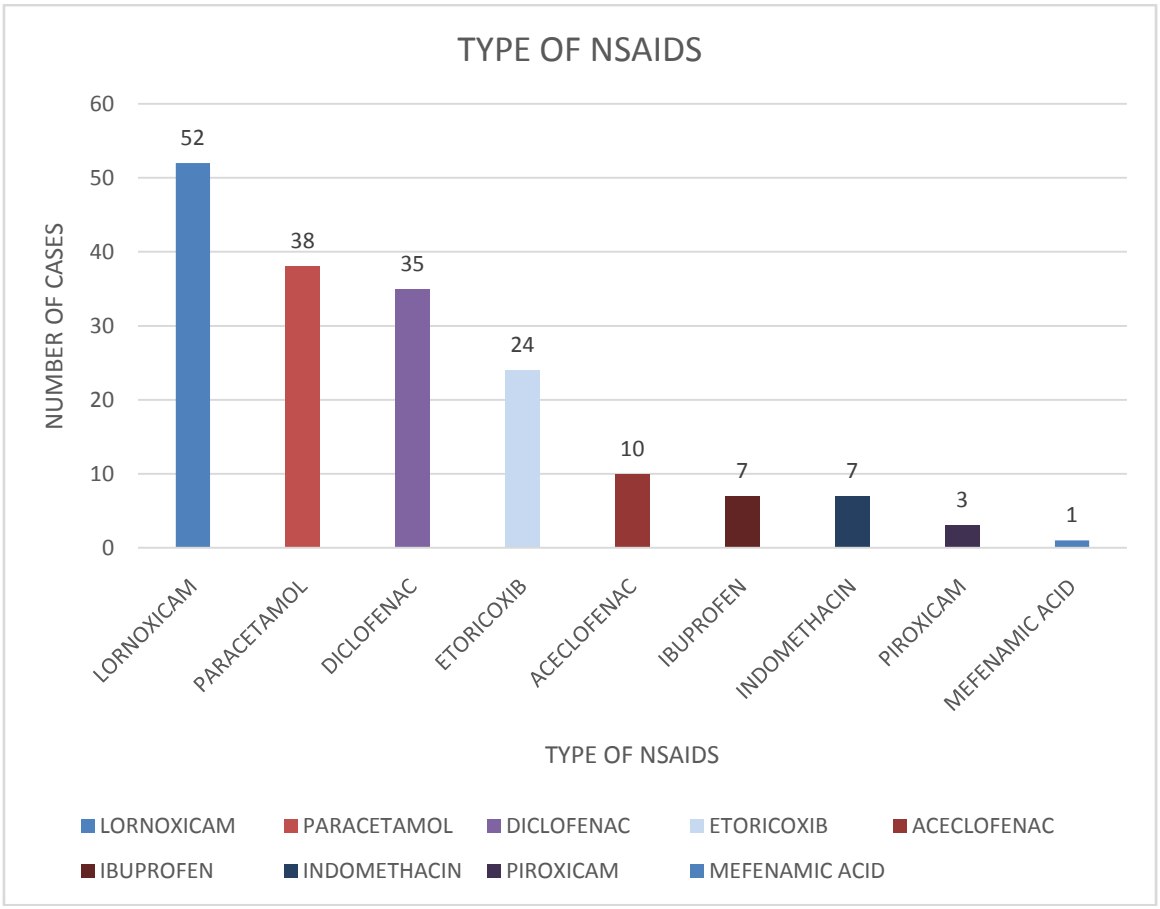

FIGURE 4: DISTRIBUTION BASED ON TYPE OF NSAIDS PRESCRIBED

5. CO-PRESCRIBED DRUGS
N=251

DRUG CLASS	NUMBER OF CASES	PERCENTAGE
H2RA	7	2.78%
PPI	91	36.25%
STEROIDS	27	10.75%
VITAMINS&SUPPLEMENTS	21	8.36%
MTX	1	0.39%
OTHER ANALGESICS	12	4.78%
MISCELLANEOUS	29	11.55%
ANTIMICROBIALS	63	25.09%

TABLE 8: DISTRIBUTION BASED ON CO-PRESCRIBED DRUGS

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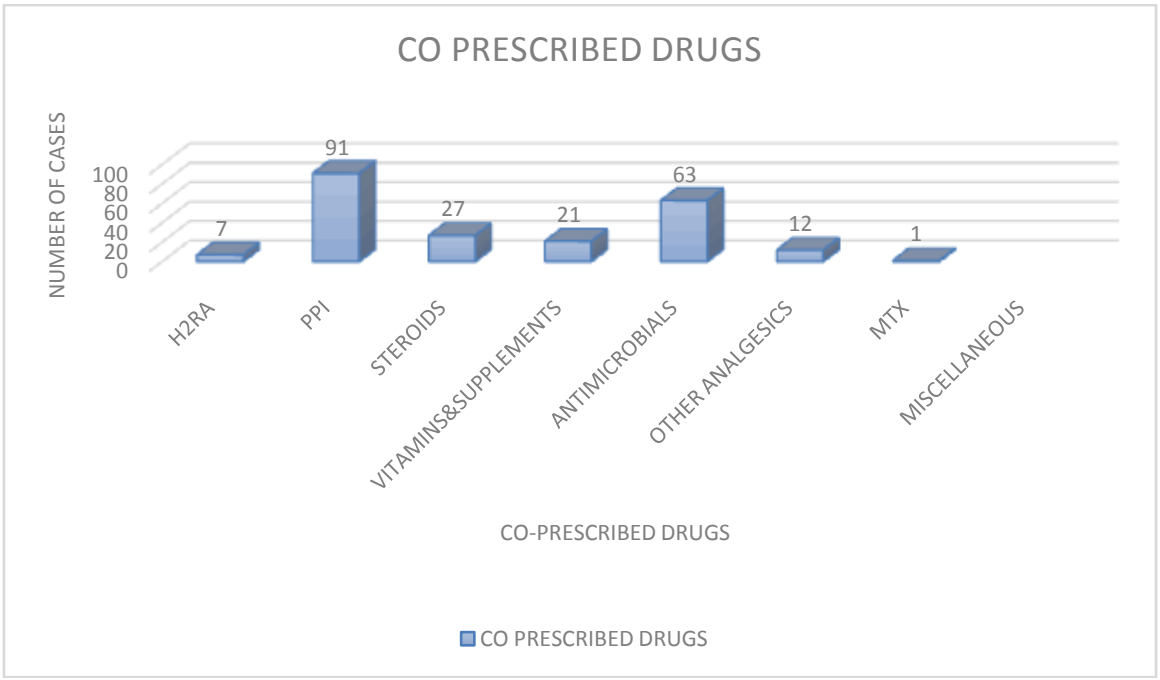

FIGURE 5: DISTRIBUTION BASED ON CO-PRESCRIBED DRUGS

6. PRESCRIPTION ANALYSIS BY MEDSCAPE

PRESCRIPTIONS	NUMBER OF CASES	PERCENTAGE
WITH DRUG INTERACTION	52	52%
WITHOUT DRUG INTERACTION	48	48%

TABLE 9:PRESCRIPTION ANALYSIS BY MEDSCAPE

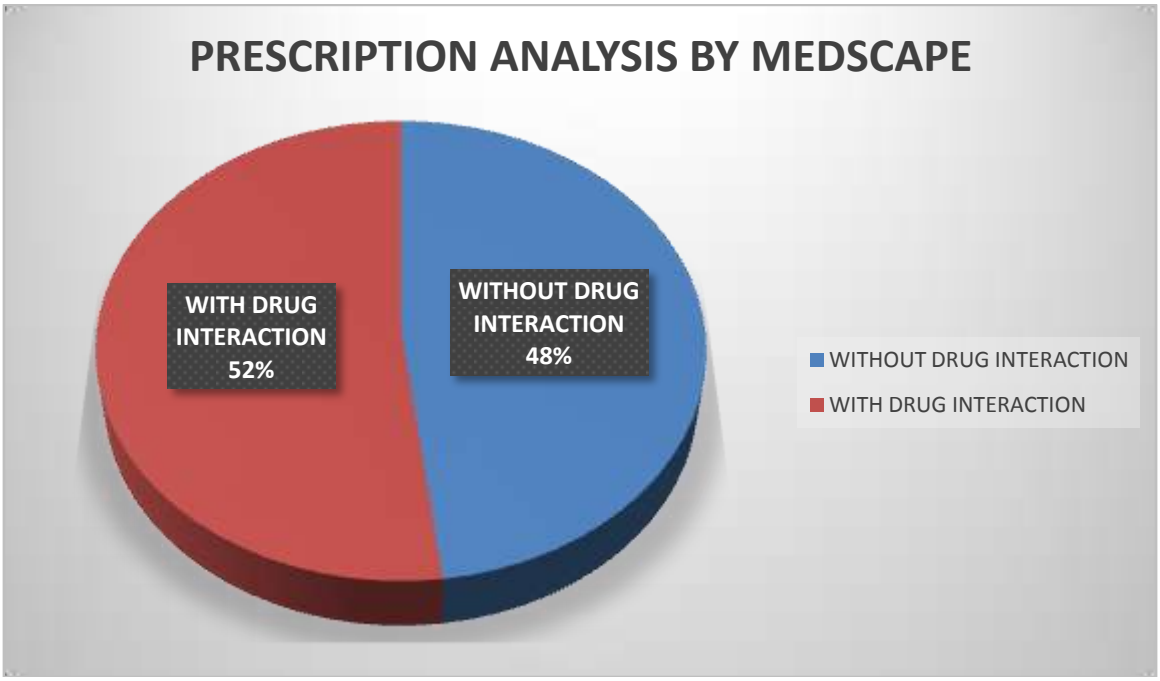

FIGURE 6: PRESCRIPTION ANALYSIS BY MEDSCAPE

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7.PRESCRIPTION ANALYSIS BY LEXICOMP

PRESCRIPTIONS	NUMBER OF CASES	PERCENTAGE
WITH DRUG INTERACTION	57	57%
WITHOUT DRUG INTERACTION	43	43%

TABLE 10: PRESCRIPTION ANALYSIS BY LEXICOMP

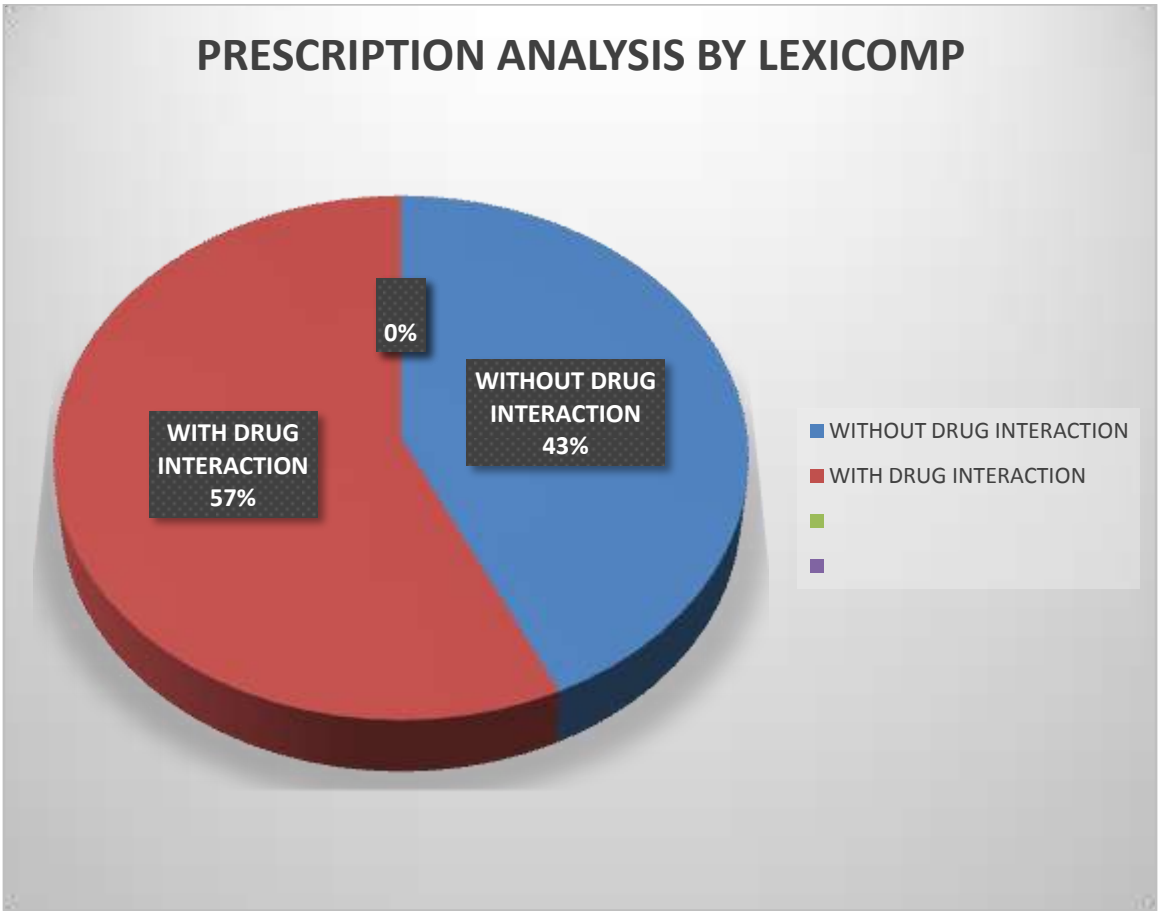

FIGURE 7:PRESCRIPTION ANALYSIS BY LEXICOMP

8.SEVERITY OF DRUG INTERACTIONS

SEVERITY OF DRUG INTERACTIONS	NUMBER OF CASES	PERCENTAGE
MAJOR	20	7.29%
MODERATE	184	67.15%
MINOR	70	25.54%

TABLE 11: DISTRIBUTION BASED ON SEVERITY OF DRUG INTERACTIONS IDENTIFIED

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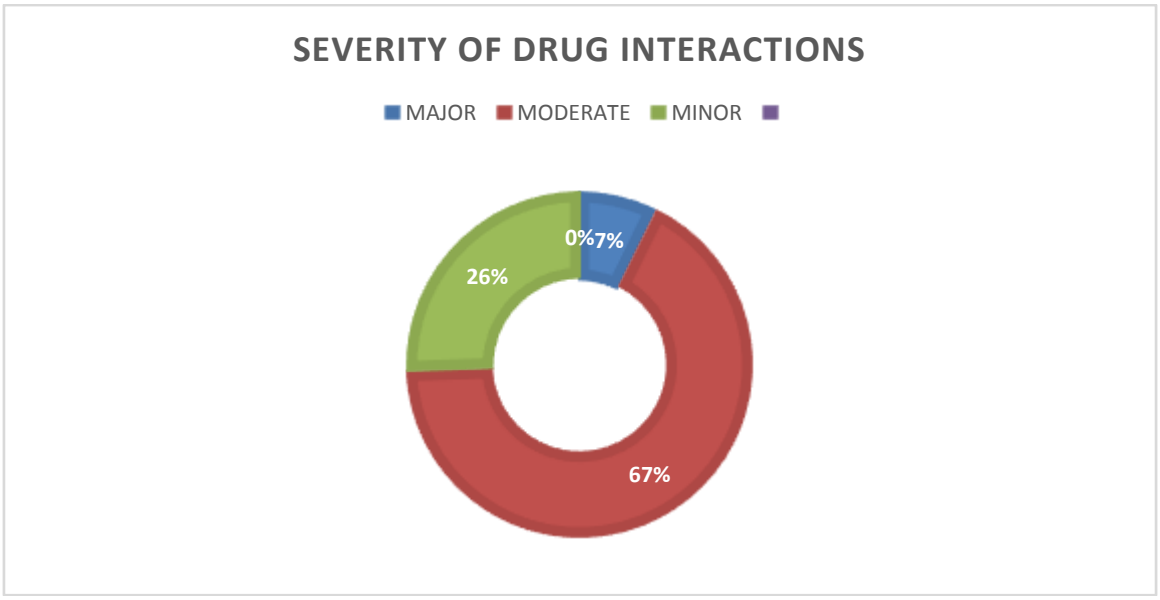

FIGURE 8:DISTRIBUTION BASED ON SEVERITY OF DRUG INTERACTIONS IDENTIFIED

9.RISK RATING BY LEXICOMP

RISK RATING	ACTION	NUMBER OF CASES	PERCENTAGE
A	No known interaction	0	0%
B	No action needed	6	5.76%
C	Monitor therapy	78	75.00%
D	Consider therapy modification	14	13,46%
X	Avoid combination	6	5.76%

TABLE 12: DISTRIBUTION BASED ON RISK RATING OF DRUG INTERACTIONS IDENTIFIED BY LEXICOMP

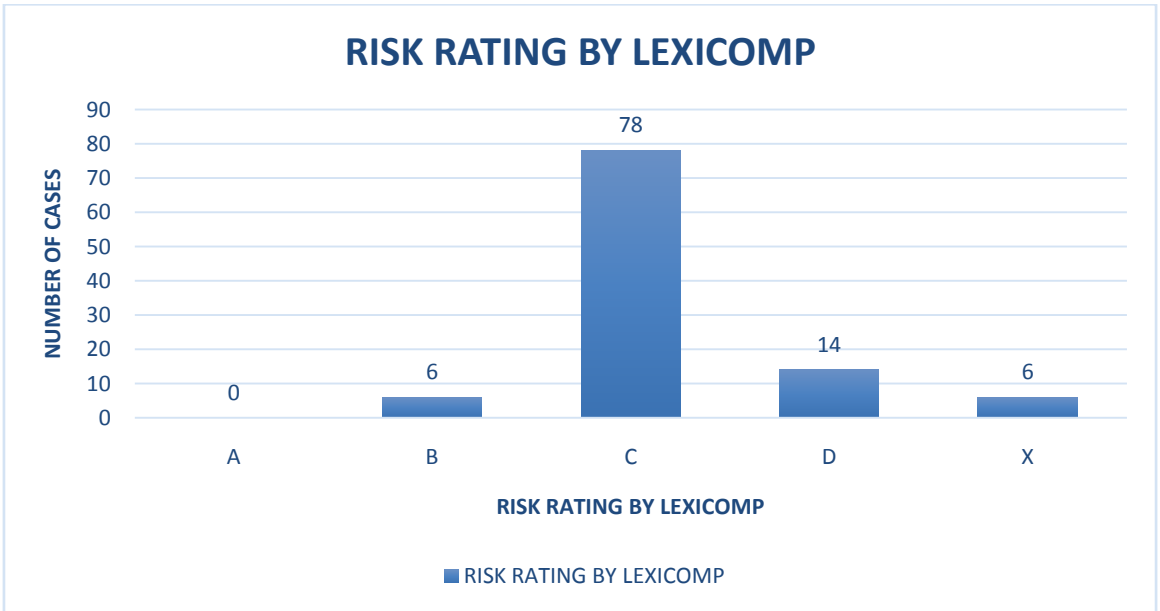

FIGURE 9: DISTRIBUTION BASED ON RISK RATING OF DRUG INTERACTIONS IDENTIFIED BY LEXICOMP

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10.FREQUENTLY INTERACTING CLASS OF DRUGS

FREQUENTLY INTERACTING CLASS	NUMBER OF CLASS	PERCENTAGE
NSAID	19	95.00%
MTX	1	5.00%

TABLE 13: DISTRIBUTION OF MAJOR INTERACTIONS BASED ON FREQUENTLY INTERACTING CLASS OF DRUGS

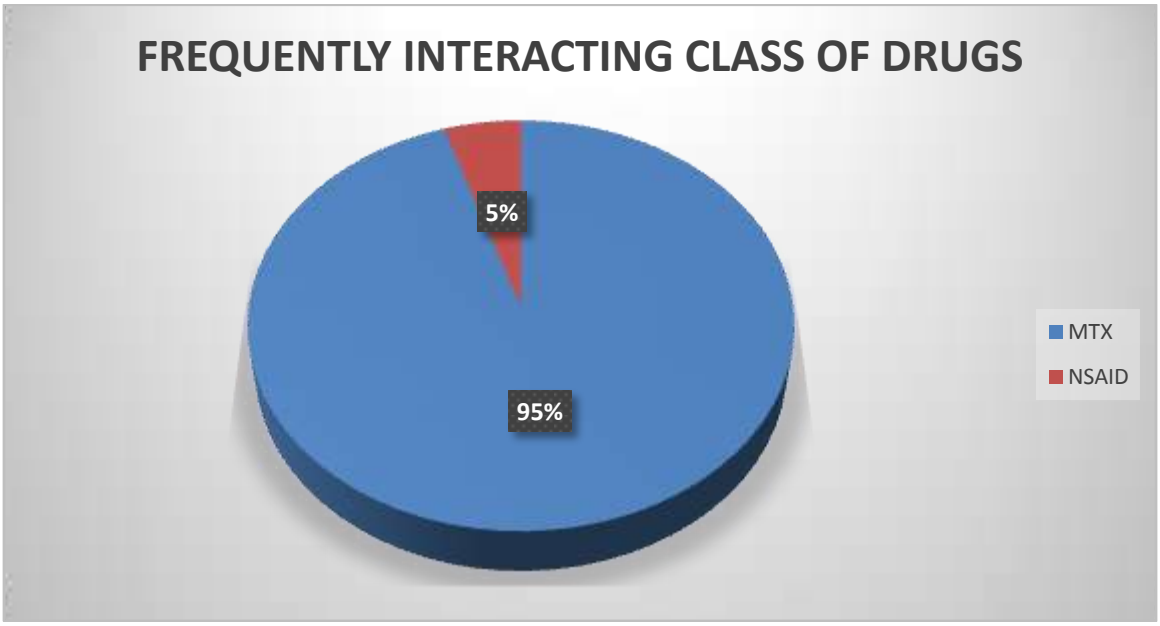

FIGURE 10: DISTRIBUTION OF MAJOR INTERACTIONS BASED ON FREQUENTLY INTERACTING CLASS OF DRUGS

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