A PROSPECTIVE OBSERVATIONAL STUDY ON DRUG UTILIZATION EVALUATION AND POTENTIAL DRUG-DRUG INTERACTION OF ANALGESIC DRUGS IN AN ORTHOPAEDIC OUTPATIENT DEPARTMENT AT TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: Primary Objective: To evaluate prescribing pattern of analgesic drugs in orthopedic outpatient department. **Secondary Objective:** To study the potential drug-drug interaction of prescribed drugs to the patient. **Methodology:** A prospective observational study was conducted after the approval of the iec of CHARUSAT. The study was conducted at IRIS Hospital, Anand, Gujarat. Participants were selected for the inclusion and exclusion criteria and those who follow the inclusion criteria were include in the study. All the details of the participant were filled in the Case Report Form (CRF) by the investigator. **Result:** A total of 450 prescriptions were analyzed, of which 41% and 59% precipitation were of males and females respectively. Age wise distributions of the patients were analyzed. Total 495 numbers of analgesic prescribed, it was observed that combination analgesic & monotherapy prescribed was 78% and 22% respectively. However, very few of the drugs were prescribed in generic name (4%). Most commonly hypertension (43.87%) comorbidity were observed. Our result found that the primary complaint of orthopaedic patients was knee osteoarthritis (OA). Most commonly analgesic prescribed in tablet (67%) formulation. Prescription were analyzed based on severity total 59% of the moderate potential DDI was observed. **Conclusion:** The study

investigated the prescribing pattern and potential Drug – Drug Interaction (DDI) of analgesics in orthopedic OPD (outpatient department) to observed, evaluate & suggested modification to improve the prescribing habits of the healthcare provider.

KEYWORDS: Prescribing Pattern, Inappropriate Drug Use, Drug interaction, WHO Prescribing Indicator.

INTRODUCTION

A systemic program called the drug utilization evaluation (DUE) system evaluates whether or not patients are given or are prescribed the right medications to improve their health state. The definition of a drug utilization evaluation is "an authorized, structured, and ongoing evaluation of prescribing, dispensing, and use of medication.[1]" Drug utilization review (DUR) or medication utilization evaluation (MUE) are other names for drug utilization evaluation.[2] Drug utilization evaluation, according to the World Health Organization (WHO), is the marketing, distribution, prescribing, and use of pharmaceuticals in society with a focus on the ensuing medical, social, and financial effects.[3] Inappropriate drug use has also been linked to increased medical expenses, the emergence of antibiotic resistance, adverse drug reactions, and patient mortality.[4,5] Orthopaedics is a subspecialty of surgery that focuses mostly on the skeletal system and treats a variety of conditions affecting the bones, tendons, and ligaments.[6] The outpatient orthopaedic department plays a significant role in the medical field.[7] Analgesic (NSAIDs, Opioids, Non-Opioids), Antibiotic, and Ulcer Protective medicines were most frequently recommended in the orthopaedic department, according to earlier study with comparable goals.[8] All medications in the analgesic family have varying degrees of analgesic, antipyretic, and anti- inflammatory effects. Except for inflammatory pain, CNS are lesser analgesics that don't cause physical reliance, don't have any misuse potential, and don't work as well. The term "non-narcotic," "non-opioid," or "aspirin-like analgesics" is also used for them.[9]

NSAIDs are the most generally prescribed class of pharmaceuticals in the world and are used as over-the- counter medications. They are the most effective treatments for the management of pain and inflammation.[10] When two or more medications interact with one another, this is known as a drug-drug interaction (DDI). This drug-drug interaction might lessen the effectiveness of your medication, result in unpleasant side effects, or intensify the effects of a certain medication.[11] DDIs are a subset of adverse drug events (ADEs) that can happen when a medication is taken and its action is changed by another medicine. Typically, the

drug's effect changes qualitatively or quantitatively as a result.[12] They may affect any drug's diagnostic, preventative, or therapeutic action and cause treatment failure, drug toxicity, or alternative drug effectiveness.[13] It may be divided into groups according on how severe it is and how medicines interact with one another.[14,15] DDIs can be mild, moderate, or severe depending on how serious they are. A serious DDIs may endanger life or result in extensive, long-lasting harm. DDI may be divided into two categories depending on the method by which medications interact with one another: pharmacokinetics and pharmacodynamics.[13] Different factors might cause possible DDIs to arise. The age of the patient, common disease states, polypharmacy, the nature of drug's pharmacokinetic and pharmacodynamics properties, the impact of disease on drug metabolism, prescriber issues like multiple prescribers prescribing the same medication, and inadequate prescriber knowledge of DDIs all contribute to the risk factor that is significantly linked to the possibility of DDI.[1,16]

MATERIAL AND METHODOLOGY

Study Site: IRIS hospital, Anand, Gujarat, India.

Duration of Study: The study was conducted for 6 months.

Study Design: Prospective Observational Study

Number of Sample Collected: The sample size is calculated using COCHRAN'S FORMULA with a standard error of 5% and confidence interval of 95%. And according to Cochran's calculation minimum sample size should be 385.

Source of Data: Data was collected from the entire orthopedic out patient's department of IRIS hospital. Required data was transcribed from patient's prescription.

Method: This study was prospective observational study. The study was carried out by evaluating prescription of the patient from orthopedic outpatient department at IRIS hospital, Anand. The patient consent will be taken for utilizing their prescription data. The patient demographic details (register no., age, gender), medical and medication history, diagnosis and drug prescribed will be collected from the prescription. The prescribed drug was recorded as- drug, dose, route, frequency, duration of therapy, indication. All the information collected by investigators.

Data Evalution: Data was analyzed using WHO prescribing indicators.

WHO prescribing indicators

I.   Average number of drugs per encounter

II. Percentage of drugs prescribed by generic name

III. Percentage of encounters with an antibiotic prescribed

IV. Percentage of encounters with an injection prescribed

V. Percentage of drugs prescribed from essential drugs list or formulary

- **Inclusion Criteria**

1. Patient's willing to participate in study

2. Patients of both gender

3. Patient of age 18 above

4. Patient attending the Orthopedic outpatient department

5. Patients taking analgesic drugs less than 6 months

- **Exclusion Criteria**

1. Patients allergic to NSAIDs or opioid drugs

2. Pregnant women

3. Patients with known drug addiction or abuse of analgesic

4. Patients with inflammatory disease (Rheumatoid arthritis, Ankylosing spondylitis)

5. Post-operative patients

6. Complementary and alternative medicine (Ayurveda and homeopathy medicine or other home remedies)

STASTICAL ANALYSIS: The collected data were entered into Microsoft excel 2013 and analyzed using Graph Pad prism 7.0 software and Microsoft office word 2013 software. Potential DDI were analyzed by using Lexicomp software. Data were analyzed using descriptive (Two-way ANOVA) statistics for the tables of frequency and its associate percentage was calculated.

RESULT AND DISCUSSION

In our study the criteria that were followed

- One patient is equal to one prescription/sample (1:1). So, 450 patients: 450 prescriptions/samples.

- According to COCHRAN'S FORMULA (with standard error of 5% and Confidence interval of 95%), minimum 385 prescriptions were carried out for this study but we analyzed 450 prescriptions.

Patients were including in the study and their prescription containing an analgesic drugs were

analyzed. The result is summarizing to study frequency of prescribing evaluation of analgesic drugs.

Table no. 1: Age Wise Distribution.

Sr. No.	Age Group	Frequency (n)	Percentage
1	18-40	85	19%
2	41-60	197	44%
3	61-80	156	34%
4	>80	12	3%

In our study prescription within the age group of 41- 60 years were in high ratio (44%), followed by prescription of age ranging between 61 – 80years (34%), age between 18-40 years (19%) and age >80 years (3%). **[TABLE N0. 1]** Similar result obtained from the study conducted by **Arohi et.al; 2020.**[57] Another study by **Abhilash et.al; 2018** which showed that the majority were male and the maximum number of patients were in the age group of 40-60 years.[18]

The result showed that out of 450 prescriptions, 41% prescription were of male and 59% of female Gender. Similar study shown **Solanki N et.al; 2019.**[19]

Table No. 2: Distribution of Prescription Based on Diagnosis.

SR. NO.	DIAGNOSIS	FREQUENCY(N=450)	PERCENTAGE
1	Knee osteoarthritis	94	20.88%
2	Back pain	90	20%
3	Knee pain	57	12.66%
4	Shoulder pain	50	11.11%
5	Muscle pain	40	8.88%
6	Spondylolisthesis	17	3.77%
7	Spine osteoarthritis	13	2.88%
8	Limber spondylosis	13	2.88%
9	Ankle pain	12	2.66%
10	Frozen shoulder	11	2.44%
11	Neck pain	11	2.44%
12	Osteoporosis	9	2%
13	Muscle spasm	7	1.55%
14	Foot pain	5	1.11%
15	Lateral epicondylitis	4	0.88%
16	Hip osteoarthritis	3	0.66%
17	Hip pain	2	0.44%
18	Leg pain	2	0.44%
19	Trigger figure	2	0.44%
20	Periarthritis shoulder	2	0.44%
21	Osteonecrosis	1	0.22%

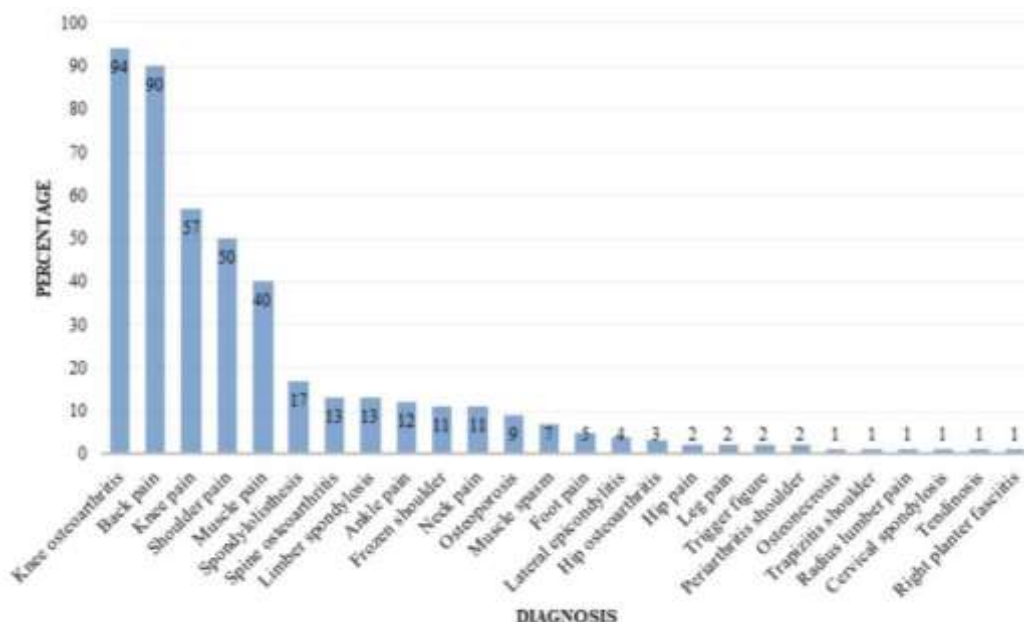| 22	Trapizitis shoulder	1	0.22%
23	Radius lumber pain	1	0.22%
24	Cervical spondylosis	1	0.22%
25	Tendinosis	1	0.22%
26	Right planter fasciitis	1	0.22%

Figure No. 1: Distribution of Prescription Based on Diagnosis.

Our result found that the primary complaint of significant number of individuals was Osteoarthritis (OA) of knee and Back pain. It was reported by 94 (20.88%) patients of OA knee and 90 (20%) patients of back pain. (As show in **TABLE NO. 2**) A study done in west Bengal by **Kumar A. et.al; 2018** reported that majority of the patients came from 18-30 years of age group. 38.5% of patients had a history of trauma. Lower back pain is the common problem among patients attended orthopaedic outpatient department.[20]

On analysis of comorbidity wise distribution of the study population, it was noted that 33.67% of patients with diabetes mellitus (DM), 43.87% of patients with hypertension (HTN), 11.22% of patients with hyperthyroidism, 3.06% of patient's hyperlipidemia with DM, 3.06 % of patient's hyperlipidemia with DM and HTN, 1.02% of patient with GERD, 2.04% of patient with hyperthyroidism and DM, and 1.02% of patient with hyperlipidemia or hyperlipidemia with asthma. the similar study conducted by **AnjaniTeja CH et al.; 2020.** Which show that 16.4% with diabetes, 21.6% with hypertension, 5.6% with thyroid disorder.[21]
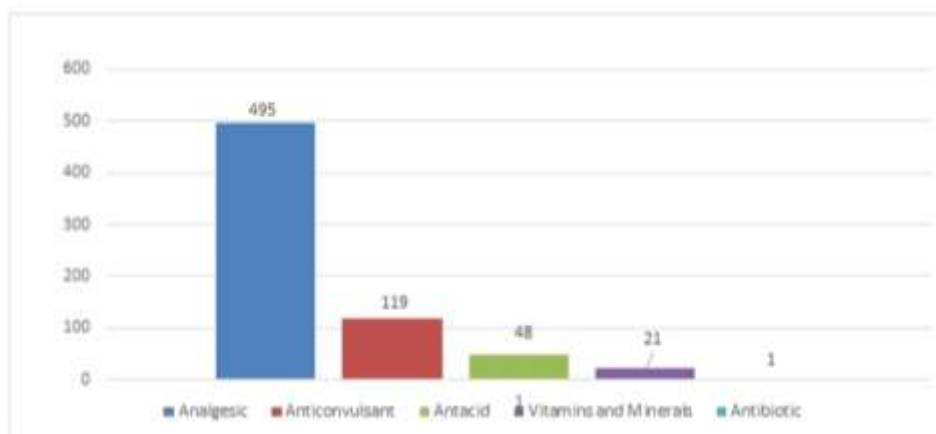
Figure No. 2: Class of Drug Prescribed In Orthopaedic Outpatient Department.

The result revealed that analgesic is choice of drug prescribed in 495 (72.36%), Vitamin and minerals 21(3.07%), Anticonvulsant 119 (17.39%), Antacid 48 (7.01%) and Antibiotic (0.14%) (As Show in **FIGURE NO-2**).

Table No. 3: The Prescription Pattern of Drug Therapy.

VARIABLES	VALUE
Combination Analgesic Therapy	383 (78%)
Monotherapy	110 (22%)
PRESCRIBED DRUG AS	
Brand Name	430 (96%)
Generic Name	20 (4%)

In our study we found that maximum number of patients were prescribed with brand name that was 96% and only 4% of drug prescribed with generic name. the similar study conducted by **Hamid Kakar et al.;2021**studies.[22]
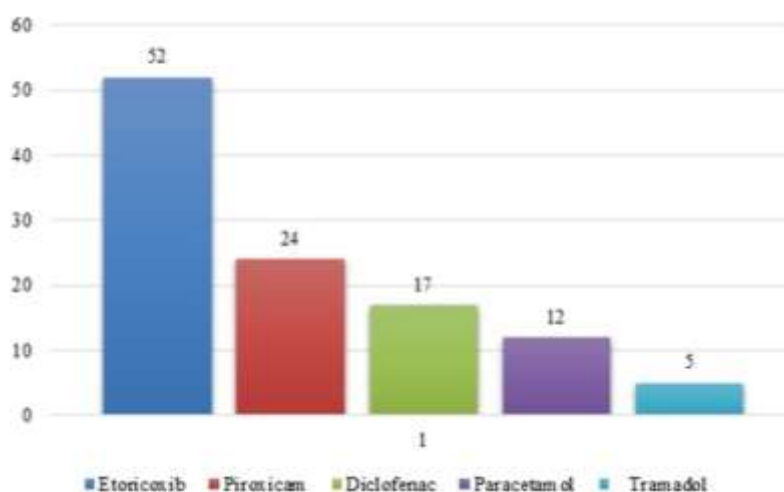

Figure No. 3: Monotherapy of Analgesic Drug.

In our study we found that maximum number of patients were treated with combination therapy (78%), over monotherapy (22%). Etoricoxib prescribed 47.27% (COX-2) and Piroxicam prescribed 21.81%, both were highly prescribed drugs in monotherapy. Most commonly prescribing analgesic drugs in monotherapy were found to be non-steroidal anti-inflammatory drugs (selective COX-2 inhibitors- Etoricoxib and COX-1 non-selective inhibitor) COX-2 inhibitor drug is most prescribed in OPD department. gastro protective agents were used in 7.027% along with NSAIDs to prevent gastro protective adverse effects. Similar study shown that **Ashok Kumar et.al; 2019** which show that gastroinstional adverse effect.[23]

Table No. 4: Fixed Drug Combination (Fdc) of Analgesic Drugs.

FDC	FREQUENCY	PERCENTAGE
NSAIDs + NSAIDs		
Diclofenac + Paracetamol	**85**	**22.13%**
Aceclofenac + Paracetamol	**44**	**11.45%**
Ibuprofen + Paracetamol	**1**	**0.26%**
Diclofenac + Paracetamol + Serratiopeptidase	**1**	**0.26%**
OPIOID + NSAIDs		
Tramadol + Paracetamol	**131**	**34.11%**
ANTI-EMETIC + NSAIDs +OPIOID		
Domperidone + Paracetamol + Tramadol	**117**	**30.46%**
NSAIDs + GLYCOSIDE		
Etoricoxib + Thiocolchicoside	**1**	**0.26%**
OTHER (gel formulation)		
Diclofenac + Linseed Oil + Methanol + Methyl Salicylate(DAN GEL)	**2**	**0.52%**
Diclofenac + Methyl Salicylate + Methanol + Alcohol(TOLAGIN GEL)	**2**	**0.52%**

Our study result show that the FDC of Tramadol with Paracetamol 131 (34.11%) was the most commonly prescribed followed by combination of Domperidone with Paracetamol and Tramadol 117 (30.46%) and Diclofenac with Paracetamol was 85(22.13%) and Aceclofenac with Paracetamol was 44 (11.45%) and Ibuprofen with Paracetamol and Etoricoxib with Thiocolchicoside was prescribed very low frequency 1 (0.26%) and other combination was prescribed as gel formation 2 (0.52%). (**TABLE NO- 4).** Combinational drugs are one of the strategies to reduce the number of drugs prescribed and improve medication compliance.[56] fixed drug compliance; concomitantly chances for adverse effects are also more. The FDCs observed in the present study were found 78%, very high in OPD practice which is similar to the findings of **Dhivya K. et al.; 2021.**[24] and **Shankar PR. Et al.; 2006.**[25]

Our study result found that out of 450 prescriptions only 25 prescription shows potential DDI. Out of 24 prescriptions 17 prescriptions has only 1 potential DDI (85%) Followed by 2 prescription has 2 potential DDI (10%) and 1prescription has 3 potential DDI (5%).

Table No. 5: Drug Interaction Analyzed Based on Severity.

SR. NO.	SEVERITY	FREQUENCY	PERCENTAGE
1	Major	2	8%
2	Moderate	14	59%
3	Minor	8	33%

In our study, a total of 24 potential drug – drug interaction was found in 450 patients, medication profiles. our study shown that major (severe) type of potential drug – drug interaction was 2(8%), moderate type of potential drug – drug interaction was 14(59%), minor type of potential drug – drug interaction was 8(33%). That similar findings were show in **Dhivya K. et al.; 2021.**[24]

Table No. 6: Potential Drug – Drug Interaction.

Sr.no	Potential Drug –Drug Interaction	Severity	Effect
1	Tramadol – Pregabalin	Major	Concurrent use of Tramadol and Pregabalin may enhance the CNS depressant effect
2	Tramadol- Clonidine	Major	Concurrent use of Tramadol and Clonidine may enhance the CNS depressant effect
3	Etoricoxib- Telmisartan + chlorthalidone	Moderate	Telmisartan and chlorthalidone may enhance the nephrotoxic effect of Etoricoxib
4	Metformin- Diclofenac	Moderate	Diclofenac may enhance the adverse/toxic effect of Metformin.
5	Metformin - Paracetamol + Tramadol	Moderate	Paracetamol and Tramadol may enhance the hypoglycemic effect of Metformin
6	Metformin - Etoricoxib	Moderate	Etoricoxib may enhance the adverse/toxic effect of Metformin
7	Tramadol - Glimepiride + Metformin	Moderate	Metformin may enhance the effect of Tramadol
8	Itraconazole – Paracetamol + Tramadol	Moderate	Itraconazole may increase serum concentration of Tramadol
9	Tramadol + Paracetamol – Telmisartan + Hydrochlorothiazide	Moderate	Tramadol may diminish the therapeutic effect of Hydrochlorothiazide
10	Teneligliptin -Tramadol	Moderate	Teneligliptin may enhance the effect of Tramadol
11	Aspirin - Diclofenac	Moderate	Diclofenac may enhance the adverse/toxic effect of Aspirin
12	Amlodipine - Etoricoxib	Minor	Etoricoxib may diminish the antihypertensive effect of Amlodipine
13	Amlodipine - Aceclofenac	Minor	Aceclofenac may diminish the

Sr.no	Potential Drug –Drug Interaction	Severity	Effect
			antihypertensive effect of Amlodipine
14	Diclofenac - Telmisartan	Minor	Telmisartan may enhance the adverse/toxic effect of Diclofenac
15	Atorvastatin - Esomeprazole	Minor	Esomeprazole may enhance the adverse/toxic effect of Atorvastatin
16	Nifedipine- Etoricoxib	Minor	Etoricoxib may diminish the antihypertensive effect of Nifedipine
17	Metformin - Rabeprazole	Minor	Rabeprazole may increase the serum concentration of Metformin
18	Amlodipine- Diclofenac	Minor	Diclofenac may diminish the antihypertensive effect of amlodipine

The maximum number of prescription had 1 drug interaction and minimum number of prescription had 3 drug interactions. Similar study conducted by **Solanki et al.; 2019**. Which was show that 44 prescriptions had the potential for possible drug interaction out of 200 prescriptions. the maximum number of drug interaction in prescription was 5 and minimum number of interactions was three.[6]

Table no. 7: Comperison Between Age Group and Prescribed Drug Using Two-Way Anova.

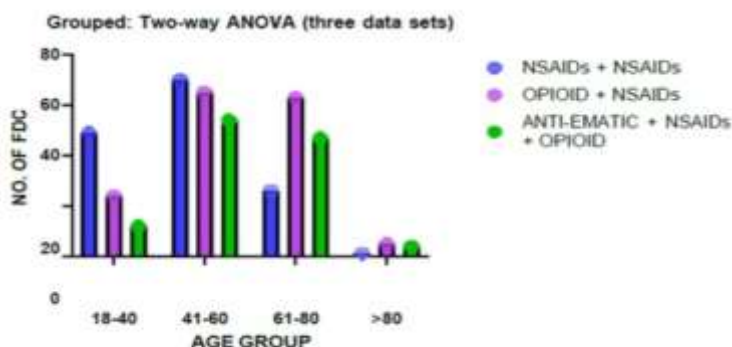| AGE GROUP	PRESCRIBED DRUG		
	NSAIDs + NSAIDs	OPIOID + NSAIDs	ANTI-EMETIC + NSAIDs + OPIOID
18 – 40	49	24	12
41 – 60	70	65	54
61 – 80	26	63	47
>80	1	5	4
ANALYSIS			
Source of Variation	% of Total Variation	P value	Significant?
AGE	79.02%	0.0131	YES
COMBINATION DRUG	2.902%	0.6399	NO

Figure No. 4: Comperison Between Age and Prescribed Drug.

ANOVA was used to analyzed the association between age groups and drug combination used. There was significant difference found in drug combination used in patient of different age group. (p value is 0.013) but no significant difference was found for drug combination used (p value is 0.6399).

Table No. 8: Comperison Between Gender And Prescribed Drug Using Two- Way Anova.

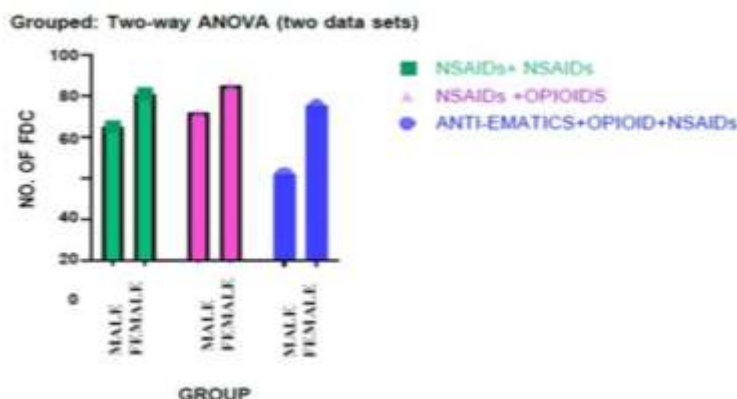| GENDER	PRESCRIBED DRUG		
	NSAIDs + NSAIDs	OPIOID + NSAIDs	ANTI-EMETICS + NSAIDs + OPIOID
MALE	65	72	42
FEMALE	81	85	75
ANALYSIS			
SOURCE OF VARIATION	% OF TOTAL VARIATION	P VALUE	SIGNIFICANT?
GENDER	54.11%	0.0800	NO
DRUG COMBINATION	36.06%	0.2141	NO

Figure No. 5: Comperison Between Gender And Prescribed Drug.

ANOVA was used to analyze the association between gender and drug combination used. There was no significant difference found in drug combination used in male and female. (p value for gender is 0.08 and for drug combination is 0.241).

Table no. 9: Who prescring indicators.

Sr. No	Who Prescribing Indicators	Percentage
1	Average number of drugs prescribed per encounter	2
2	Percentage of encounters with an antibiotic prescribed	0.1%
3	Percentage of drugs prescribed by generic name	2.60%
4	Percentage of encounter with an injection prescribed	0.65%
5	Percentage of drugs prescribed from essential drugs list or formulary	100%

The 450 prescriptions obtained during the study were analyzed using WHO prescribing indicators and 768 drugs were prescribed totally average number of drugs per encounter was 2. Total number of analgesics prescribed was 495. Percentage of encounter with an antibiotic prescribed 0.1%. Percentage of drug prescribed by generic name were 2.60%. Percentage of encounter with injections prescribed were 0.65%. Percentage of drugs prescribed from essential drugs list 100%. (As show in **TABLE NO. 9.)** Similar finding was shown in **Dhivya k. et al.; 2021.**[24] According to the findings of the current study, analgesics are the more commonly given drugs in orthopaedic outpatient department, every patient was prescribed analgesics followed by antacids medicines and vitamin supplements. In current study, we found that number of prescribed drugs in relevantly lower than that reported in previous study. The average (mean) number of drugs per prescription is an important parameter while doing a prescription audit.[25] In our study according to WHO prescribing indicator average number of drugs per encounter was 2 drugs. The similar findings were a hospital-based study in India had reported a mean number of two drugs by **Hede SS et.al;1987.**[26] The mean number of drugs was more than two in other studies reported in the literature.[27,28] According to WHO guideline on rational use of drugs per prescription is 1.6 – 1.8.[28] In a previous study finding show that average number of drugs per prescription was 3-4. The similar findings were reported in several countries (Indonesia, Niger, Nigeria, India, Ghana, and Pakistan) in which three or more drug were prescriber per prescription.[29,30]

CONCLUSION

The present study has reported that the most commonly prescribed drugs were analgesics, gastro protective agents, minerals and vitamin and anti – convulsant. Our study concludes that average drugs encountered per patient were normal and physicians are suggested to prescribe drugs in their generic name only. Drug utilization and prescribing quality should be improved by promoting medical education and current updates to the doctors. Pharmacists should participate actively in updating drug information to the physicians and other health care professionals. A periodic audit should be conducted by a clinical pharmacist to reduce an error in the prescription.

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