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Research Article

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Drug Utilization Review on Non-Steroidal Anti-Inflammatory Drugs

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Abstract: In India, any prescription generally has an NSAID. According to our knowledge many of the studies were done on NSAID's hence, the present study is carried out to know the usage and prescribing patterns of NSAID's. The information generated from the study might be supportive to communicate with the prescribers and advice the various gaps noticed for improving the prescribing patterns for best patient outcomes, and the information also helps in outlining further studies. Thus it ultimately benefits the patients in minimizing the incidences of drug interactions with NSAID's if any and adverse effects caused due to NSAID's. The aim of the paper is to conduct a retrospective observational study in a tertiary care teaching hospital to assess demographic and clinical variables like drug interactions associated with NSAID administration, for the 6 months in all departments except Paediatrics. All patients of various age groups who have received NSAID's therapy from all departments were included by giving pre-informed consent in our study. Prescribing patterns were observed and analyzed in 300 patients during the study period. Among 300, 162 were males and 138 were females. Out of all, 36 patients were from age group >70, 50 patients were from age 61-70, 51 patients from age 51-60, 49 patients from 41-50, 48 patients from 31-40, 56 patients from age 21-30 and 10 patients from age 11-20. A social history of every patient was collected and analyzed where 56 were smokers, 244 were non-smokers and 72 were alcoholics, 228 were non-alcoholics. Paracetamol was the most widely used drug of about 42%. We found 11.22% major drug interactions, 37.75% moderate interactions and 51% minor interactions. Statistical analysis one way ANOVA was done in SPSS version 21software, and the result was of significant difference between NSAID's treatments. Two way ANOVA was done which showed variability in gender groups with treatment regard to NSAID's is due to chance attributed to effects of gender or effect of treatment. Though many drugs are prescribed lucidly in India, not much differences are found in prescriptions given by healthcare professionals, and in prescribing patterns. To promote better patient compliance and to detect the adverse drug reactions early, involvement of clinical pharmacist helps more in prescribing the drugs rational.

Keywords: Drug utilization evaluation (DUE), non-steroidal anti-inflammatory drugs (NSAID s), statistical analysis.

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1. INTRODUCTION

Non Steroidal Anti-Inflammatory Drugs are most frequently recommended drug classes of remedies for pain and inflammation, They will take position roughly 5-10% in every prescription. 96% of patients over 65 years of age are using NSAIDs more prevalently. Relatively 7.3% of elder patients over 60 years of age holds minimum of one NSAIDs in their prescription in an year[1]. In addition to their medication result, NSAIDs have antipyrexic and analgesic properties. These medications inhibit Cyclooxygenases (COXs) enzymes, that measures rate-determining enzymes for prostaglandins and alternative prostanoids synthesis, like thromboxanes. Compared with Nonselective NSAIDs that inhibit each Cox and cyclooxygenase, cyclooxygenase inhibitors (as referred to as coxibs) inhibit solely cyclooxygenase enzymes. cyclooxygenase plays a vital role in autocoid mediate pain and inflammation, whereas Cox plays some work role within the protection of internal organ tissue layer and in blood platelet hemostasia, whereas the gastro enteric safety profiles of cyclooxygenase inhibitors have improved, the cardio-nephrotoxic adverse effects measure still vital. Several known adverse effects of NSAID's includes gastro intestinal toxicity, cardiovascular adverse effects, nephrotoxicity, however some contemporary literatures reveal that anti- inflammatory effects of NSAIDs inturn improves the cognitive functions[2]. Currently, drug utilization studies (DUS) are used as a potential alpha tool within the analysis of health care systems and to establish the role of medication in society. They produce a sound socio-medical, health and economic bottom work for health care systems. Drug utilization review (DUR) is defined as an authorized, structured, ongoing review of prescribing, dispensing and use of medication. These are also called as Drug Utilisation Studies (DUS) or Medical Utilisation Evaluation(MUE)[3]. It suggests a comprehensive review of a patient's medication and health history before, during, and when dispensing to gain clear patient outcome and for better therapeutic decision making[4]. Pharmacists collaborating in DUR programs will directly improve the standards of patient care, severally and as populations, to rule out the improper drug therapy, stop adverse drug reactions and improve overall drug effectiveness. DUR intention is to aid the rational use of medication in populations. In individual patients, rational drug use implies the prescription of a more-documented drugs in accomplishing the ideal dose on the right indication at a right value[5]. It is vital to understand that inappropriate use of medication represents a possible hazard to the patients associated with worthless expenses. It is troublesome to perceive the rational use of drugs while not the information on however medication are being prescribed. The prime target of the study is to analyse the DUR of NSAIDs in the midst of patients from various departments from Andhra hospitals, Vijayawada. Prolonged use of NSAIDs increases the danger of adverse effects. So the study implies to elevate patient safety by keeping an eye on prescribing pattern. The point is to encourage the reasonable utilization of medications in population. In individual patients, the sound medication use suggests the remedy of a well-recorded medication in an ideal portion on the right sign at a moderate cost [6,7]. It is critical to understand that improper utilization of medications speaks to the potential danger to the patients and a pointless cost. It is hard to comprehend the reasonable utilization of medication without the learning of how medications are being recommended. The aim of our study paper is to conduct a retrospective observational study in a tertiary care teaching hospital to assess demographic and clinical variables like drug interactions associated with NSAID administration, for the 6 months in all departments except Paediatrics.

2. MATERIALS AND METHODS[8]

2.1 Study site

The study is a retrospective, observational study which was carried out in various departments of Andhra Hospital, a tertiary care teaching hospital in Vijayawada, Andhra Pradesh.

2.2 Study Design & Duration

The study was planned and carried out for a period of six months from September 2018 to February 2019 in various departments of a tertiary care hospital. 300 subjects who are inpatients for at least 2 days and who are taking NSAID's were selected by getting pre-informed consent for study from the patients. This study was approved by Institutional human ethics committee with register number IHEC/SIMS/2018/025.

2.3 Study Criteria

2.3.1 Inclusion Criteria

All the patients of various age groups who received any category of NSAID in all the departments were included except paediatrics. Patients containing prescription of any disease from in-patient department taking NSAID's of both sex, with hospital stay of minimum 2 days.

2.3.2 Exclusion Criteria

Patients not willing to participate in study, lactating women, paediatrics, HIV, cancer chemotherapy and out patients were excluded from the study.

2.4 Study Population

About 300 subjects who are inpatients for at least 2 days and who are taking NSAID's were selected with pre-informed consent for study. This study was carried out for a period of 6 months in various departments of the tertiary care hospital. This study was approved by Institutional human ethics committee with register number IHEC/SIMS/2018/025. All data was collected from patient records and noted, using a suitably designed data collection form[9]. All the cases/prescriptions were reviewed retrospectively and monitored extensively for utilization pattern of non steroidal anti-inflammatory drugs like their category, rationality of the prescription, indication and number of drugs in prescriptions[10,11]. Drugs prescribed were rigorously analysed for drug interactions and for other parameters by using drug interaction checker available from Medscape, Drugs.com, Clinirex.

3. STATISTICAL ANALYSIS

The data was statistically analyzed using SPSS version 21. Descriptive statistics such as frequency, percentages, valid percentages, cumulative percentages, mean, and standard error were calculated for related variables. Cross tabulation

of the data was done where ever required. In univariate analysis, categorical variables are computed using chi-square test. One way and two way ANOVA were performed for required variable[12] like smoking, alcohol consumption.

4. RESULTS AND DISCUSSION

A total of 300 patients were enrolled in the study out of which 162 patients were male and 138 patients were female as shown in Table 1. Study found that majority of the males were using NSAID's with about 54% when compared to females of about 46% given in table .1

Table 1: Basic Demographic Details

Gender	Frequency	Percent	Cumulative Percent
Male	162	54%	54%
Female	138	46%	100%
Total	300	100%	--

Table 1.1 Age of the patients taking NSAID's

Age	Frequency	Percent	Cumulative percent
0-10yrs	0	0	0
11-20yrs	10	3.3	3.3
21-30yrs	56	18.6	21.9
31-40yrs	48	16	37.9
41-50yrs	49	16.3	54.9
51-60yrs	51	17	71.2
61-70yrs	50	16.6	87.8
>70yrs	36	12	100

Among the 300 patients, 56 patients were of age group of 21-30 years, and 51 patients were of age group 51-60 years and 50 patients were of 61-70 years of age group and 49 patients were of 41-50 years age group and 48 patients were of 31-40 years of age group and 36 patients were from >70 years age group and 10 patients were from 11-20 years of age group[13]. Percentages of age group under NSAID treatment are given in Table 1.1. Cross tabulation of age groups with gender are shown in Table 2.

Table 2: Age v/s Gender Cross tabulation

Age	Gender		Total
	Male	Female	
0-10yrs	0	0	0
11-20yrs	2	8	10
21-30yrs	29	27	56
31-40yrs	28	20	48
41-50yrs	30	19	49
51-60yrs	28	23	51
61-70yrs	23	27	50
>70yrs	21	15	36
Total	161	139	300

In the Table 3, Age group along with their use of particular NSAID is differentiated

Table3: Age VS Treatment

AGE	Aceclo -fenac	Diclo -fenac	Aspi -rin	Parace -tamol	Etori -coxib	Mefena -mic acid	Napro -Xen	Ibupro -fen
0-10yrs	0	0	0	0	0	0	0	0
11-20yrs	2	2	3	8	0	3	0	2
21-30yrs	5	5	1	23	0	4	0	0
31-40yrs	5	5	7	32	1	4	2	0
41-50yrs	4	3	17	23	1	2	3	2
51-60yrs	2	2	21	17	0	1	2	0
61-70yrs	2	2	25	11	1	3	0	0
>70yrs	3	2	22	13	0	2	0	0
Total	23	21	96	127	3	19	7	4

4.1 Smoking associated with NSAID use[14]

Table 4: Smoking associated with NSAID use

NSAID	Smoker	Non smoker	Total
Aceclofenac	6	17	23
Diclofenac	4	17	21
Aspirin	14	82	96
Paracetamol	24	103	127
Naproxen	4	3	7
Mefenamic acid	1	18	19
Etoricoxib	2	1	3
Ibuprofen	1	3	4
Total	56	244	300

Out of 300 cases, social history of each patient was collected and analysed. We found that 56 patients are smokers and 244 patients are non-smokers. Differentiation of number of smokers and non-smokers using particular NSAID's are shown in Table 4. Usually drugs have side effects if the patient is a smoker, so monitoring is required. The study tried to find out the association between steroid treatment and smoking habit shown in Table 4.1. We did pearson chi-square statistical procedure in SPSS software version 21 and the significance value was found to be 0.028 which states that NSAID treatment is dependent on smoking habit of patients.

4.2 Chi-Square Tests

Table 4.1: Association of smoking with NSAID treatment[15]

	Value	Df	Asymptotic Significance (2-sided)
Pearson Chi-Square	15.726[a]	7	.028
Likelihood Ratio	13.471	7	.061
No of Valid Cases	300		

a. 8 cells (50.0%) have expected count less than 5. The minimum expected count is .56.

P value is less than LOS 0.05. So, study rejected the null hypothesis. This value of chi-square indicates that there is association between the smoking and NSAID treatment taken by the patient. That indicates NSAID treatment is dependent of smoking habit of patients[13].

4.3 Alcoholics associated with NSAID Treatment

Out of 300 cases, social history of each patient was collected and analysed. We found that 72 patients are alcoholics and 228 patients are non-alcoholics. Differentiation of number of alcoholics and non alcoholics using particular NSAID's are shown in Table 5. Usually many drugs have interactions with alcohol, so monitoring of drug levels should be done if required. The study tried to find out the association between NSAID treatment and alcohol habit shown in Table 5.1. We did pearson chi-square statistical procedure in SPSS software version 21, which states that steroid treatment is independent on alcohol consumption of the patients [16,17].

Table 5: Alcohol associated with NSAID Treatment

Drug	Alcoholic	Non alcoholic	Total
Aceclofenac	3	20	23
Diclofenac	3	18	21
Aspirin	29	67	96
Paracetamol	33	94	127
Naproxen	2	5	7
Mefenamic acid	1	18	19
Etoricoxib	1	2	3
Ibuprofen	0	4	4
Total	72	228	300

4.4 Chi-Square Tests

Table no 5.1 Association of alcohol with NSAID treatment

	Value	Df	Asymptotic Significance (2-sided)
Pearson Chi-Square	10.047[a]	7	.186
Likelihood Ratio	12.444	7	.087
N of Valid Cases	300		

a. 6 cells (37.5%) have expected count less than 5. The minimum expected count is .72

P value is more than the LOS 0.05. Therefore study failed to reject the null hypothesis. There is no association between alcoholics and NSAID's treated patients, revealed by the results of chi-square test. This indicates that NSAID treatment is independent on alcohol consumption of the patients[18].

4.5 *System involved v/s NSAID taken by patients[19]*

Table 6: System associated with steroid use

Systems involved	Aceclofenac	Diclofenac	Aspirin	Paracetamol	Naproxen	Mefenamic acid	Ibuprofen	Etoricoxib	Total
Skeletal	9	10	1	16	0	0	0	0	36
Respiratory	0	1	7	33	0	1	0	0	42
Reproductive	12	0	9	23	0	14	0	0	58
Renal	2	1	3	0	0	0	0	0	6
Nervous	0	0	33	20	4	1	1	1	60
Muscular	1	4	0	2	0	0	3	0	10
Digestive	0	0	3	23	0	0	0	0	26
Endocrine	1	0	5	0	0	0	0	0	6
Vascular	0	7	37	6	3	1	0	2	56
Total	25	23	98	124	7	16	4	3	300

4.6 *Systems associated with NSAID's usage*

In this study patients with disorders in different systems were enrolled. Out of 300 cases 60 patients with disorder in nervous system use NSAID's and 58 patients with disorder in reproductive system use NSAID's and 56 patients with disorder in vascular system and 42 patients with Respiratory disorder and 36 patients with disorder in skeletal system, 26 patients with digestive system disorder, 10 patients with disorder in muscular system, 6 patients with renal disorder and 6 patients with endocrine system disorder are reported using NSAID's. Differentiation of particular NSAID used in disorder of particular system was shown in table 6.

4.7 *NSAID v/s Diagnosis Cross tabulation*

Table 7: Diagnosis associated NSAID use

NSAID	General medicine	Cardiology	Gynaecology	Gastrology	Orthopaedic	Neurology	Pulmonology	Total
Aeclofenac	2	0	12	0	9	0	0	23
Diclofenac	6	0	0	0	14	0	1	21
Aspirin	5	37	10	3	1	33	7	96
Paracetamol	4	2	26	23	18	21	33	127
Naproxen	3	0	0	0	0	4	0	7
Mefenamic acid	0	1	16	0	0	1	1	19
Etoricoxib	0	2	0	0	0	1	0	3
Ibuprofen	3	0	0	0	0	1	0	4
Total	23	42	64	26	42	61	42	300

4.8 Diagnosis associated NSAID use[20]

In this study, after analysing 300 prescriptions with NSAID's founded that 23 patients are from General Medicine, 42 patients are from cardiology department, 64 patients are from Gynaecology department, 26 patients are from Gastroenterology department, 42 patients are from Orthopaedics department, 61 patients are from neurology department, 42 patients are from Pulmonology department. The study founded the association between diagnosis and NSAID treatment by performing pearson chi-square statistical method in SPSS version 21 software, results are shown in the Table 7 that NSAID treatment is dependent on department of its use.

4.9 *Co morbidities of patients under NSAID treatment*

Table 8: Co morbidities of patients under NSAID treatment

Comorbidities	Aceclofenac	Diclofenac	Aspirin	Paracetamol	Ibuprofen	Naproxen	Mefenamic acid
Diabetes mellitus	17	8	29	16	1	1	2
HTN	12	6	18	34	0	1	3
Heart disease	0	0	42	2	1	1	1

Kidney disease	2	1	3	0	0	0	0
Liver disease	3	1	3	20	0	0	0
CVA	0	0	14	17	1	4	1
Pneumonia	0	1	0	6	0	0	1
Thyroid Disorder	0	0	3	2	0	0	16
Arthritis	2	14	0	6	1	0	0

4.10 Co morbidities of patients under NSAID treatment

A total of 300 prescriptions were analysed during the study period and details of co morbidities of each case were also noted and the results showed that out of 300 cases using NSAID's 74 cases have Hypertension, 74 cases have Diabetes, 47 cases have heart diseases, 6 cases have kidney diseases, 7 cases have liver diseases, 37 cases have Cerebro-Vascular Disorder, 8 cases have Pneumonia, 21 cases have Thyroid disorders, 23 cases have Arthritis. We found that the major co-morbidities were in most of the cases of Hypertension and Diabetes. As these both may lead to further complications, NSADIs should be used carefully to prevent any side effects. The dose and use of NSAID's should be carefully monitored in patients with co-morbidities. Differentiation of NSAID's used in different co-morbidities of patients was shown in Table 8[21].

4.11 Drug interactions with NSAID's

In this Drug Utilisation Review (DUR), 300 prescriptions with NSAIDs were analysed. In the studied cases and drugs analysed in the prescriptions, we found DDI (Drug Drug Interactions). Out of 127 patients using Paracetamol we found 32 interactions and 96 patients using Aspirin we found 48 interactions, 21 patients using Diclofenac we found 8 interactions, 19 patients using Mefenamic acid we found 4 interactions, 23 patients using Aceclofenac we found 6 interactions. Percentage of Drug Drug Interactions (%DDI) was shown in Table 9.

Table 9: Drug interactions with NSAID's

Groups	NSAID's	No. of patients	No. of DDI	% of DDI
A	Aceclofenac	23	6	6.12%
B	Diclofenac	21	8	8.16%
C	Aspirin	96	48	48.97%
D	Paracetamol	127	32	32.65%
E	Mefenamic acid	19	4	4.08%

4.12 NSAID – Drug Interactions based on severity [22,23]

Differentiating incidence of DDI according to severity is presented in Table 10. In this study total incidence of major interactions are 11 (7 interactions with Aspirin, 3 interactions with Paracetamol, 1 interaction with Diclofenac) and total incidence of moderate interactions are 37 (20 interactions with Aspirin, 10 interactions with Paracetamol, 2 interactions with Aceclofenac, 2 interactions with Diclofenac, 3 interactions with Mefenamic acid) and total incidence of minor interactions are 50 (21 interactions with Aspirin, 19 interactions with Paracetamol, 6 interactions with Diclofenac, 2 interactions with Aceclofenac and 2 interactions with Mefenamic acid) were found from a total Drug interactions of 96 as shown in the Table 10. The above values reveals the competitive incidence of more important drug-drug interactions, which notifies that monitoring is required and change in therapy is necessary according to their significant level. No toxic or adverse effects of NSAID's are found in this study.

Table 10: NSAID – Drug Interactions based on severity

Groups	NSAIDs	Major	Moderate	Minor
A	Aceclofenac	0	2	2
B	Diclofenac	1	2	6
C	Aspirin	7	20	21
D	Paracetamol	3	10	19
E	Mefenamic acid	0	3	2
F	Ibuprofen	-	-	-
G	Naproxen	-	-	-

4.13 One way ANOVA for Treatments [24,25]

In this study, statistical procedure of One way ANOVA was done in SPSS version 21 software, to find out whether there is any difference between the Treatments. We got a result of significance 0.00 which was less than our Level Of Significance (LOS) 0.05, indicating that there was significant difference between the NSAID treatments. The results of the test were shown in Table 11.

Table 11: One way ANOVA for Treatments					
Source of Variation	*SS*	*Df*	*MS*	*F*	*P-value*
Between Groups	18.39077	1	18.39077	11.41651	0.000825
Within Groups	480.0459	298	1.610892		
Total	498.4367	299			

Sig 0.00 < LOS 0.05 which indicates that there is significant difference between treatments.

4.14 Two Way Anova For Gender Vs Treatment

In this study, we performed a statistical procedure of Two way ANOVA among the two variables Gender and NSAID Treatment using SPSS version 21 software and the result showed that variability is observed in the gender groups with treatment with regard to NSAID's is due to chance and it cannot be attributed to effects of gender or the effect of Treatment. The results of the test were shown in Table 12.

Table 12: Two Way Anova For Gender VS Treatment				
Source	**Sum of Squares**	**Df**	**Mean Square**	**F**
Treatment	7750	7	1107.143	17.6537
Gender	36	1	36	0.5740
Error	439	7	62.71429	
Total	8225	15		

F table values for d.f (7,7) and (1,7) are 17.6 and 18.22 which shows Fcal < Ftab this proves that variability observed in gender groups with treatment with regard to NSAID's is due to chance it cannot be attributed to effects of gender or effect of treatment[26]. The mean and standard error of NSAID treatment are given in table no 12.1.

4.15 NSAID Treatment

Table 12.1 shows the means and standard error of NSAID treatment at the level of 95% confidence interval.			
Drugs	**Mean**	**Std. Error**	**N**
Aceclofenac	1.609	1.03	23
Aspirin	1.454	1.73	97
Diclofenac	1.667	0.77	21
Etoricoxib	1.333	0.4	3
Ibuprofen	1.750	0	4
Mefenamic Acid	1.947	0.063	19
Naproxen	1.429	0.26	7
Paracetamol	1.317	0.18	126
Total	1.457	7.12	300

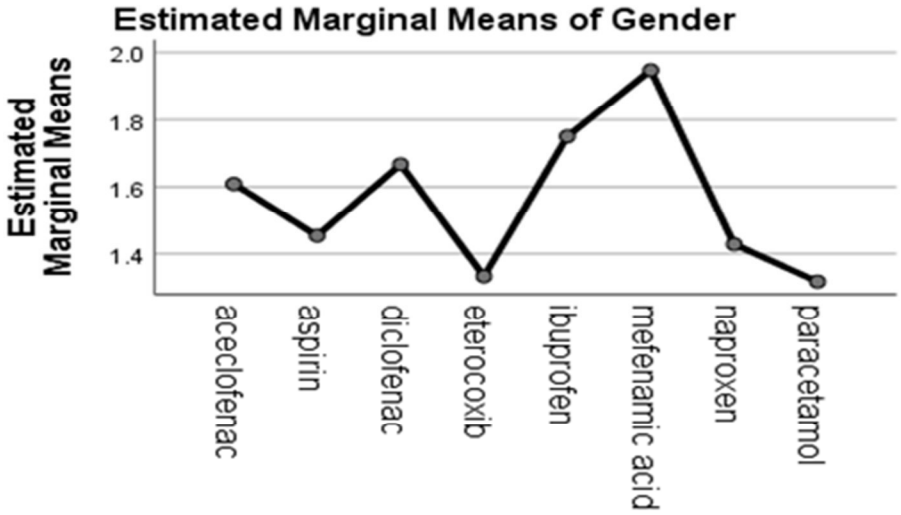
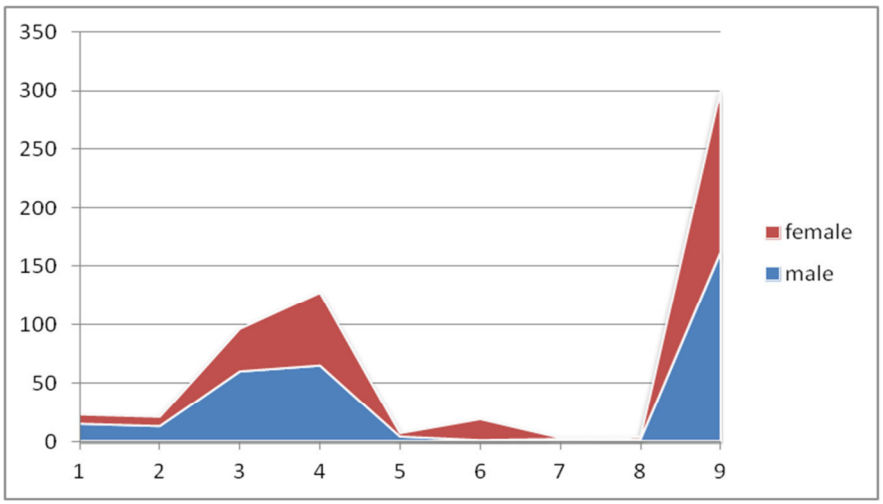


Fig 1. shows the graphical representation of estimated marginal means of Gender using different NSAID's.



(Aceclofenac, Diclofenac, Aspirin, Paracetamol, Naproxen, Mefenamic acid, Etoricoxib, Ibuprofen)

Fig 2. Shows the stacked graphical representation of gender distribution of male and female patients on NSAID treatment. This graph represents the NSAID's taken by gender wise distribution. Blue indicates Male. Red indicates Female. X- axis indicates NSAID drugs.

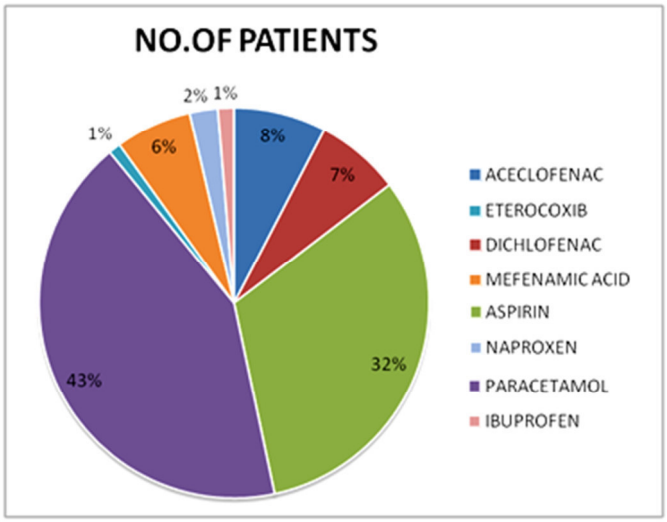


Fig 3. Shows the pie chart of NSAID's used for treatment in the 300 cases of this study. Major part of the pie graph was covered by Paracetamol (127), Aspirin (96), Aceclofenac (23), Diclofenac (21), Mefenamic acid (19), Naproxen (7), Ibuprofen (4), Eterocoxib (3).

Study reveals majorly NSAID's are taken by females, but drugs like naproxen, mefenamic acid and etoricoxib are only consumed by females but not by males, given in fig.2. Majorly paracetamol is consumed given in Fig. 3 and the least consumed drug is etoricoxib. The irrational use of drugs (e.g. inadequate dose or polypharmacy) may lead to failure of therapy or drug interactions/adverse reactions and increases the cost of therapy /mortality. This will increase the adverse effects and can lead to dependence on these medications. Our study reveals the majority of NSAIDs are received by males than females. In the patients of age group 21-30 years they recieve more NSAID's than other age groups of patients. For smoker patients NSAID's show certain side effects and for alcoholics, they develop drug interaction which requires drug monitoring. Applying the data to Pearson chi-square statistical procedure in SPSS software version 21 which results in NSAID treatment is dependent on smoking habits and independent on alcohol consumption and it is dependent on the system using. Major co-morbidities are found to be in hypertension and diabetes cases. Out of all drugs, Aspirin was showing major drug interactions. Applying statistical analysis indicates that there is a significant difference between NSAID treatments. Gender and NSAID Treatment results showed that variability is observed in the gender groups with treatment, with regard to NSAID's are due to chance and it cannot be attributed to effects of gender or the effect of Treatment. So, urgent steps are required to eliminate the root of this problem at the earliest. The clinical pharmacist has a major role in promoting the NSAID's utilization rationally, by educating and promoting the evidence-based practice guidelines.[27]

5. CONCLUSION AND FUTURE PERSPECTIVE

This type of DUR studies improves the prescribing patterns of NSAID's. They can be performed on drugs with greater ADR profiles, poly pharmacy and concurrent therapies. Thus, the rational drug therapy can be achieved to ensure best positive patient outcomes.

6. ACKNOWLEDGEMENTS

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Andhra hospitals, Vijayawada, India for giving their immense support to carry out this work.

7. AUTHORS CONTRIBUTION STATEMENT

Madhuri latha thadanki conceived the idea, guided this research project and reviewed the manuscript. Ayesha ahmadi contributed in literature search, data collection and data analysis. K.geetha mounika contributed in study design and writing, P.pravallika contributed in literature search, data collection and data curation.

8. CONFLICTS OF INTEREST

Conflict of interest declared none.

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