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STUDY OF VARIATION IN PRICE OF VARIOUS NSAIDS COMBINATIONS AVAILABLE IN INDIAN MARKET

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ABSTRACT: Introduction: Non Steroidal Anti Inflammatory drugs are widely used drugs worldwide for various inflammatory conditions and acute as well as chronic pain conditions. In India large number of NSAIDs preparations are available in the market. Therefore choosing a NSAID becomes very difficult task for the prescribing physician. **Objective:** To evaluate the price variation of the different NSAIDs preparation available in the Indian market. **Material And Methods**: Cost of a particular drug in the same strength and dosage forms being manufactured by different companies was obtained from "Current Index of Medical Specialties" (CIMS) Jan-Apr, 2015 and "Indian Drug Review" (IDR) Issue 1,2015. Difference between the maximum and minimum cost of the same drug manufactured by different pharmaceutical companies was calculated and percentage cost variation was calculated. Spearman correlation analysis and regression coefficient was done to observe the correlation between no. of manufacturing companies and their percentage price variation with the help of IBM Statistical Package for Social Sciences (SPSS v.21). **Result:** NSAIDs combination were commonly found as Oral and Topical combination formulations. Out of 33 different Oral Combination with 70 various formulations, maximum %variation in cost were 3400 [Aceclofenac 100mg+Paracetamol 500mg tab], 300.62 [Dexibuprofen 300mg+Paracetmol 500mg tab] and 400 [Diclofenac Na 50mg+Serrapeptase 10mg tab] with average %variation in cost 107.4%. For Topical Combination Formulations, only 5 formulations of 2 drugs with 86 different pharmaceutical companies were found. From which, Diclofenac topical combination formulation show highest %variation in cost [192.59] with average %variation in cost being 55.63. **Conclusion**: Our findings revealed that the prices of various NSAIDs shows great variation. Some measures must be taken by the government to bring about the uniformity in the price

INTRODUCTION: Non steroidal anti inflammatory drugs (NSAIDs) are the most used and abused drugs in the world today (annually about 20,000 tonnes of Aspirin is consumed in United States alone). Pain and fever being the most common complaints, these drugs naturally are in great demand and doctors have no hesitation to cater to this.[1]

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They are also widely prescribed to relieve the symptoms of a variety of inflammatory diseases, including osteoarthritis (OA), rheumatoid arthritis (RA), and gout, as well as other conditions characterized by acute pain.[2] Indian drug industry, always ready to cater to the 'needs' of medical professionals and always in the forefront of developing mixtures and combinations of various kinds, has responded very well to this 'demand'.[1]

In India, a variety of NSAID combinations are available, often as Over-The-Counter products. These combinations are the easiest way of selling two drugs when one (or even none) may be needed for the patient. These combination pills have now

become the largest selling 'brands' of antiinflammatory/analgesic/antipyretic products. The 'single' drugs have almost become redundant and 'old fashioned'.[1] Today if the market share of 'NSAID combination pills', the great invention of the Indian drug industry, is much bigger than that of individual drugs, it speaks volumes of our irrational prescribing habits. (The 'combined pills' of Ibuprofen+Paracetamol now have a much bigger market share than ibuprofen alone, which was once the No. 1 NSAID sold in India) [1]

In the absence of a clear, comprehensive and rational drug policy, the production of pharmaceutical preparations in India is grossly distorted. Thus, Indian markets are flooded with over 70,000 formulations, compared to roughly 350 preparations listed on the WHO Essential Drugs List. There are thousands of drug companies, and several companies manufacture generic preparations using different brand names.[3]

In the developing countries like India, the cost of drugs is a major concern to both physician and patient and an important factor influencing compliance with treatment. Differential pricing could potentially be a very effective strategy to improve access to essential medicines in low and middle-income countries where most patients pay for medicines out-of pocket and therefore cannot afford the prices compared to high income markets.[4]

In the Indian market NSAIDS combinations are available in different formulations. This creates a lot problem with physician to decide the drug of choice for individual patients and the price of these combination drugs becomes an important issue for the developing country like India. Therefore the aim of our study is to analyse the cost variation in the NSAIDs group combinations available in the Indian market.

MATERIAL AND METHODS:

Cost of particular NSAIDs group combinations in the same strength and dosage forms being manufactured by different pharmaceutical companies was obtained from "Indian Drug Review" [IDR] issue 1 2015 and "Current Index Of Medical Specialties" [CIMS] Jan-Apr 2015. The drug prices available in IDR and CIMS were compared, as they are readily available source of drug information which are updated regularly. The drugs, price of which were not given the IDR and CIMS or the drugs being manufactured by only one company were excluded from analysis. Difference between maximum and minimum cost of the same drug manufactured by different pharmaceutical companies was calculated.

Percentage cost variation was calculated as follows: Cost Variation (%) = Max cost-Min cost/Min cost*100 [5]

Spearman correlation analysis and regression coefficient was done to observe the correlation between no. of manufacturing companies and their percentage price variation with the help of IBM Statistical Package for Social Sciences (SPSS v.21).

RESULTS:

NSAIDs combination were commonly found as Oral combination formulations [**Table 1(a), 1(b**) and **1(c)]** and Topical combination formulations [**Table 2**].

TABLE 1(a): ORAL COMBINATION FORMULATIONS

Drug [No. of Formulations]	Dose & Dosage formulations	Number of manufacturing companies	Minimum Cost (INR)	Maximum Cost (INR)	% Variation in Cost
Aceclofenac+Serrapeptase [2]	100mg+15mg tab [10]	10	35	67.6	93.14
Aceclofenac+Rabeprazole [1]	200mg+20mg Cap [10]	3[1]	79	85	7.59
Aceclofenac+Paracetamol [5]	100mg+325mg tab [10]	38[4]	16	60	275
	100mg+500mg tab [10]	113[12]	10	350	3400
	100mg+650mg tab [10]	3	27.38	29.5	7.74
	100mg+325mg FC tab [10]	3	33.5	36	7.46
	100mg+ 500mg FC tab [10]	18	13.71	43	213.6
	50mg+125mg Susp [60 ml]	4	38	55	44.73
	50mg+125mg/5ml Susp [60 ml]	5[1]	29.9	37.5	25.41

	50mg+125mg Syrup [60 ml]	3	37.5	39	4
Aceclofenac+Paracetamol+Serrapeptase [2]	100mg+ 325mg+15mg tab [10]	28[3]	36	90	150
	100mg+500mg+15mg tab [10]	43[6]	29.9	80	167.6
	100mg+ 500mg+10mg tab [10]	18[4]	43.9	69	57.17
	100mg+325mg+10mg tab [10]	8	59	89	50.84
	100mg+500mg+15mg FC tab [10]	7	41.8	59.5	42.34
	100mg+325mg+15mg FC tab [10]	4	30	70	133.3
Aceclofenac+Paracetamol+Serrapeptase EC [2]	100mg+500mg+15mg tab [10]	3	39	50.16	28.61
	100mg+500mg+15mg FC tab [10]	3	39	48.5	24.35
	100mg+325mg+15mg FC tab [10]	2	64	65	1.56
Lornoxicam+Paracetamol [2]	8mg+ 500mg tab [10]	28[7]	39.9	89	123.1
	8mg+325mg tab [10]	9[2]	60	120	100
	4mg+500mg tab [10]	6[1]	42	85	102.4
	4mg+500mg FC tab	3	45	48	6.66
	8mg+500mg FC tab	3	65	73	12.3
Mafenamic Acid+ Paracetamol [4]	500mg+325mg tab [10]	2	29	29	0
	500mg+450mg tab [10]	3	25	29.5	18
	100mg+250mg/5ml Susp [60 ml]	2	40	42	5
	50mg+125mg/5ml Susp [60 ml]	5	31	35	12.9
	50mg+125mg Syrup [60 ml]	2	36	36	0
	50mg+125mg/5ml Syrup [60 ml]	2	32	36	12.5
Mafenamic Acid+Dicyclomine HCl [1]	250mg+10mg tab [10]	5[2]	20	25	25

*Price were not written.

TABLE 1(b): ORAL COMBINATION FORMULATIONS

Drug [No. of Formulations]	Dose & Dosage formulations	Number of manufacturing companies	Minimum Cost (INR)	Maximun Cost (INR)	% Variation in Cost
Naproxen Na+Domperidone [2]	250mg+10mg tab [10]	2	39	49	25.64
Nimesulide+Paracetamol [3]	100mg+325mg tab [10]	20[3]	16	36.3	126.87
	100mg+350mg tab [10]	3	23	34.5	50
	100mg+500mg tab [10]	64[4]	16	58	262.5
Nimesulide+Paracetamol+Serratiopetidase [2]	100mg+500mg+10mg tab [10]	2	53	57	7.54
	100mg+500mg+15mg tab[10]	2	39	42.5	8.97
Nimesulide+Serratiopetidase [3]	100mg+10mg tab [10]	17[2]	45	72	60
	100mg+15mg tab [10]	13[2]	39	73.4	88.2
	100mg+15mg FC tab [10]	4[2]	34.56	52	50.46
	100mg+10mg Cap [10]	2	59.5	64.5	8.4
	100mg+15mg Cap [10]	2	59.8	60.9	1.83
Nimesulide+Diclofenac Na [3]	100mg+ 50mg Cap [10]	2	21	21	0
	100mg+50mg SG Cap [10]	2	25	31	24
Etoricoxib+ Paracetamol [1]	60mg+500mg tab [10]	3	69.1	73	5.64
Etodolac+ Paracetamol [3]	400mg+325mg tab [10]	3[1]	85	145	70.59
	400mg+500mg tab [10]	4[2]	71.5	92	28.67
	400mg+500mg tab ER [10]	2	125	145	16
Ibuprofen+Paracetamol [5]	100mg+125mg tab [10]	2	2.92	3.9	33.56
	100mg+125mg P tab [10]	2	3.88	6.5	67.52
	100mg+125mg Susp	2	10.7	10.9	1.86

	[60ml]				
	100mg+125mg/5ml Susp [60ml]	8	9.3	23.5	152.68
	100mg+162.5mg/5ml Susp [60ml]	8	10.4	17.2	65.38
	100mg+162.5mg/5ml Susp [100ml]	2	21.2	22	3.77
	400mg+325mg tab [10]	17	6.3	13.5	114.28
	400mg+325mg Cap [10]	2	6.45	8.17	26.66
	400mg+333mg tab [10]	2	5.62	12.9	129.53
	400mg+500mg tab [10]	13	6.89	15	117.7
Ibuprofen+Paracetamol+Caffeine [1]	400mg+500mg+25mg tab [10]	2	8.2	19.7	140.24
Dexibuprofen+Paracetmol [1]	300mg+500mg tab[10]	2	16.1	64.5	300.62

*Price were not written.

TABLE 1(c): ORAL COMBINATION FORMULATIONS

Drug [No. of Formulations]	Dose & Dosage formulations	Number of manufacturing companies	Minimum Cost (INR)	Maximun Cost (INR)	% Variation in Cost
Diclofenac+Serrapeptase [3]	50mg+10mg tab[10]	10[2]	42	69	64.28
Diclofenac K+Rabeprazole Na [1]	100mg+20mg SR cap[10]	2	49	75	53.06
Diclofenac Na+Serrapeptase [1]	50mg+10mg FC tab[10]	2	63	104	65.07
	50mg+10mg tab[10]	14	39	195	400
	50mg+10mg EC tab[10]	2	66	71	7.57
Diclofenac K+Serrapeptase [2]	50mg+10mg tab[10]	60[7]	39	90	130.76
	50mg+15mg FC tab[10]	2	52	54	3.84
	50mg+15mg tab[10]	5[1]	55	69	25.45
Diclofenac+Trypsin+Bromelain+Rotoside [1]	50 mg+48mg+90mg+100 mg EC tab [10]	3[1]	155	155	0
Diclofenac+ Paracetamol [1]	50mg+325mg tab[10]	4	11.1	22.5	102.7
Diclofenac K+ Paracetamol [3]	50mg+325mg tab[10]	6[1]	20	28	40
	50mg+500mg tab[10]	12[4]	10	40	300
Diclofenac Na+ Paracetamol [4]	50mg+325mg tab[10]	7	15	27	80
	50mg+500mg tab[10]	39[3]	7.95	38.8	388.05
	75mg+225mg/3ml[3ml] Inj	2	9.7	16.6	71.13
	25mg+75mg[3ml] Inj	2	15	15	0
Diclofenac K+ Paracetamol+Chlorzoxazone [1]	50mg+325mg+250mg tab[10]	3[1]	41	44	7.31
Diclofenac K+ Paracetamol+Serratiopeptidase [2]	50mg+325mg+10mg tab[10]	15[2]	52	97	86.53
	50mg+325mg+15mg tab[10]	4	60	72	20
	50mg+500mg+10mg tab[10]	13[1]	57	76	33.33
	50mg+500mg+15mg tab[10]	5	56	71	26.78
Diclofenac Na+ Paracetamol+Chlorzoxazone [1]	50mg+325mg+250mg tab[10]	3	27	34	25.92
Diclofenac K+ Paracetamol+Serratiopeptidase [1]	50mg+500mg+10mg tab[10]	3	62	72	16.12
Paracetamol+Promethazine HCl [2]	125mg+5mg Syr[60ml]	5[1]	22.5	39	73.33
	125mg+2.5mg/5ml Syr[60ml]	2	17	34.5	102.94
Paracetamol+Dl methionine [3]	125mg+12.5mg/5ml Susp[60ml]	2	22.5	34.8	54.66
Paracetamol+Caffeine [1]	650mg+50mg tab[10]	2	18.2	22.5	23.62

*Price were not written.

TABLE 2: TOPICAL COMBINATION FORMULATIONS

Drug [No. of Formulations]	Dose & Dosage formulations	Number of manufacturing companies	Minimum Cost (INR)	Maximun Cost (INR)	% Variation in Cost
Aceclofenac Combination [2]	Aceclofenac 1.5%w/w T Gel [30gm]	12	32	60	87.5
Diclofenac Combination [3]	Aceclofenac T Gel [30gm]	2	45.8	45.8	0
	Diclofenac diethylamine 1.16% w/w T:gel[10g]	4	20	23	15
	Diclofenac diethylamine 1.16% w/w T:gel[15g]	2	15	35	133.33
	Diclofenac diethylamine 1.16% w/w T:gel[30g]	31[1]	27	79	192.59
	Diclofenac diethylamine 1.16% w/w T:gel[30g]	2	85	90	5.88
	Diclofenac diethylamine 1% w/w Ointment[30g]	2	58	58	0
	Diclofenac diethylamine 1.16% w/w Ointment[30g]	3	38	65	71.05
	Diclofenac diethylamine 1.16% w/w Spray[20g]	2	46	47	2.17
	Diclofenac diethylammon 1.16% w/w T:gel[30g]	14[1]	36	65	80.55
	Diclofenac diethylammon 1.16% w/w T:gel[25g]	2	33	56	69.69
	Diclofenac T:gel[30g]	2	30	35	16.66
	Diclofenac Na 1% w/w T:gel[30]	8[1]	45	67	48.88

*Price were not written

In case of Oral combination formulations, we have evaluated total 33 combinations of 70 different formulations manufactured by different pharmaceutical companies. [**Table 1(a), 1(b), 1(c)**]. Maximum combinations were found with Diclofenac [21] followed by Aceclofenac[12] and Nimesulide[11].

The Paracetamol and Serratiopeptidase were commonly being added as a combination drug. Other drugs commonly added as combination drug were: Rabeprazole, Dicyclomine HCL, Domperidone, Caffeine, Chlorzoxazone etc. The maximum %variation in cost seen with 3400[Aceclofenac 100mg+Paracetamol 500mg tab], 300.62[Dexibuprofen 300mg+Paracetmol 500mg tab] and 400[Diclofenac Na 50mg+Serrapeptase 10mg tab] in Table 1(a),1(b),and 1(c) respectively .The average %variation in cost in Our study was 107.4.

For Topical Combination Formulations [**Table 2],** only 5 formulations of 2 drugs with 86 different pharmaceutical companies were found. Diclofenac topical combination formulation shows highest %variation in cost [192.59]. The average %variation in cost was being 55.63.

DISCUSSION: Our findings revealed a great difference in the cost of various NSAIDs combinations available in the market. Most commonly used drugs like paracetamol, diclofenac, ibuprofen etc. showed a wide difference in the cost which is shocking. An average percentage variation in the cost for the oral and topical combination formulations were 107.4 and 55.63 respectively.

Maximum difference in the cost was found with the combinations of aceclofenac, diclofenac, ibuprofen, lornoxicam, nimesulide and paracetamol which was above average [>100%]. How a common person could afford this much difference? As we know these drugs are commonly used in acute pain as well as chronic pain conditions, cost and rationality becomes important factors in determining the patient compliance well as patient safety to the therapy.

Drug prices are controlled according to drug price control order 2013 (DPCO). Drug price control order (DPCO) is an order issued by the government, to fix prices of drug. Once medicine is brought under DPCO, it cannot be sold at a price higher than that, fixed by the government. In India, in 1979, 80-85% of the drugs in the market were under price control and the number has slowly decreased in subsequent years.[6] But surprisingly there is not a single NSAIDs combination under DPCO. A distorted market structure, Skewness of information, raw material costs, government regulation and pricing policies also could be the possible reason for this price variation as evident from the literature.[7, 8]

Spearman rank correlation (r_s=0.81) (R^2=0.67) revealed interesting result. We observed that a significant positive correlation exists between the number of manufacturing companies and the percentage price variation. Regression coefficient was also done to evaluate the fact that as the number of manufacturing company's increases the percentage price variation also increases. Our results showed that there is an urgent need of controlling price variation among different brands of available NSAIDs agents.

Increasing pharmaceutical costs negatively impacts patients in two ways. First, high direct expenses for those of limited resources may mean a choice between medicines and necessities such as food or clothing. Alternatively, patients who do not take their medicine as directed or go without the potentially beneficial therapies entirely often suffer negative health consequences unfortunately, patients may be too embarrassed to tell their physicians when they cannot afford their medicines. [1]

The 19th WHO Model List of essential medicines (April 2015) and the National list of essential drugs of India (2011) has included many FDCs.[9, 10] But there is no any single NSAIDs combination in the WHO EML 2015 as well as NLEM 2011 India.

Unfortunately many FDCs being introduced in India are usually irrational. There is no justification in combining one NSAID (nimesulide, diclofenec, ibuprofen) with another NSAID (paracetamol) having same pharmacological actions. The most pressing concern with the FDCs is that they expose patients to unnecessary risk of adverse drug reactions. The increased risk of hepatotoxicity has been reported due to the use of combination of nimesulide with paracetamol. There is increased risk of nephrotoxicity with NSAIDs combinations.[11, 12] Still there has been increase in the irrational FDCs in the recent past by leaps and bounds and many of them available as over the counter (OTC) drugs. [13]

Banned drugs are still available in developing countries like India due to lack of law enforcement and physician awareness. The government needs to enforce laws and provide information to physicians and patients regarding these drugs through drug information centres. The pharmacist should hold public information campaigns and educate consumers, and thus play an important role on eliminating the market for banned drugs. [14]

The following steps can be taken to improve the rationality and decrease the cost variation:

1. The hit and trial method of combining drugs should be replaced by a rational and logical basis for bringing out a fixed dose drug formulation. [11]

2. There is a need to strengthen the mechanism for continuing professional development of practitioners to ensure that they have the necessary knowledge and skills to prescribe rationally.[11]

3. The doctor must choose the drug on the basis of cost and rationality rather than the on the basis of claims done by various pharmaceutical companies.

4. Medical education must provide training to the medical and postgraduate students as they are the future of any country.

5. The last and the important one that frequently prescribed NSAIDs combination must be included in the Essential medicine list and kept under price control by DPCO.

CONCLUSION:

Our findings revealed wide variation the price in the different NSAIDs combinations. As the NSAIDs are widely used drugs, their cost should be affordable by the common man. So these drugs should be included in the Essential medicine list and brought under price control with DPCO as well

as their combination should be made taking into consideration the rationality for the combination with regard to particular disease condition.

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