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A Study Using the Defined Daily Dose Method to Evaluate the Use of Antihypertensive Medications

Kaustav Ghosh[1], Afreen Nasir[2], Avinash HR[3]

[1,2]Doctor of Pharmacy, Department of Pharmacy Practice, Acharya & BM Reddy College of Pharmacy, Bengaluru, Karnataka, India.
[3]Assistant Professor, Department of General Medicine, ESIC MC-PGIMSR, Rajajinagar, Bengaluru, Karnataka, India

ABSTRACT:
The DDD concept is a method for quantifying a drug. Drug use in terms of DDD aids in converting the number of pharmaceuticals readily available into medically significant units and in estimating the number of people who have been exposed to a specific drug or class of drugs. In a hospital setting, the unit DDD per 100 bed-days suggests the proportion of inpatients that may receive a DDD. DDD in anti-hypertensive medications helps to track down prescription drug usage and examine drug usage trends. A 6-month prospective and observational study was conducted to assess the drug utilisation of antihypertensives. In this study we found that Diuretics were commonly prescribed antihypertensives. Furosemide and Spironolactone were mostly prescribed antihypertensives as single therapy, while Telmisartan+Hydrochlorothiazide was commonly prescribed as combination therapy. Propranolol was over utilised antihypertensives with 187.82 DDD/100bed-days and 1.74 PDD:DDD ratio.

Keywords: Drug Utilisation Evaluation, Defined Daily Dose, Anatomical Therapeutic Chemical, Prescribed Daily Dose, Antihypertensive Agents.

INTRODUCTION

Drug utilisation research is a crucial component of pharmacoepidemiology since it explains the scope, makeup, and factors that influence drug exposure. Studies on drug usage shed light on trends in drug use. The findings increase our understanding of effectiveness and safety. It also provides information on the cost-effectiveness of medicines. This study can be used to determine the level of drug use in a certain location or even how much the substance is being misused or overused. The ATC and DDD approaches aid in meeting the aforementioned requirements. DUE Studies assist us in achieving the goal of responsible and productive drug usage in society.

The Anatomical Therapeutic Chemical (ATC) classification system serves as an international standard for classifying drugs based on the organ or system on which they act as well as their therapeutic, pharmacological, and chemical properties. Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults whereas Prescribed Daily Dose (PDD) is the average daily dose of drug prescribed in the prescription. The DDD methodology has

the benefits of being able to monitor drug exposure, being affordable, simple to use, and allowing integration with other databases.

Hypertension is a prevalent illness that accounts for a large portion of cardiovascular disease and premature mortality in contemporary society. According to estimates from the World Health Organization (WHO) from 2013, hypertension is the third most common cause of death worldwide and a significant public health issue, accounting for one in every eight fatalities. Non-communicable illnesses are a significant cause of death in India, where they account for 10% of all fatalities. In India, the average prevalence of hypertension is 25% in urban areas and 10% in rural areas. A significant risk factor for stroke and cardiovascular disease is hypertension. It is responsible for 10% of all ischemic heart disease, 21% of all peripheral vascular disease, 24% of all acute myocardial infarctions, and 29% of all strokes. It was calculated that 29,8% of Indians have hypertension overall.[1]
One of the most significant classes of medications that doctors frequently prescribe in hospitals is an antihypertensive medication. This study offers insights into the scope of antihypertensive medication use and current prescription trends. It also gives an estimate of the socioeconomic toll that high blood pressure and its related comorbidities take.

MATERIALS AND METHODS

This is a prospective observational study conducted for a period of 6 months in the Department of General Medicine, ESIC MC-PGIMSR, Rajajinagar, Bengaluru. A total of 285 inpatients enrolled in our study from March 2022 to August 2022 who were prescribed with antihypertensive drugs. Patients of ≥18 years of age of either gender were included in the study. Lactating and pregnant women were excluded. The patient's profile and treatment details were collected from the case sheet and medication charts using a self-designed data collection form after obtaining approval from the IEC committee of ESIC MC-PGIMSR.
Statistical analysis was performed and DDD/100 bed-days was calculated using the given formula.

$$\text{Drug Usage (Defined Daily Dose)}^{[2]} = \frac{\text{Number of items used} \times \text{Amount of drug per item (mg)}}{\text{WHO recommended DDD of drug}}$$

$$\text{DDD/100 bed-days}^{[2]} = \frac{\text{No. of units of drug prescribed during the study period x 100}}{\text{DDD} \times \text{No. of days in study period} \times \text{No. of beds} \times \text{Bed occupancy}}$$

RESULTS

During the study period, 285 patients who were prescribed with antihypertensive agents were enrolled in our research study from the in-patient department of General Medicine ward at ESIC Medical College, PGIMSR & Model Hospital, Rajajinagar, Bengaluru. On total 8519 prescriptions were analyzed. Out of 285 study subjects, majority of patients (27.72%) were in the age group of 50-59 years as in Table 1 and majority of study subjects were male 178 (62.46%).

Table 1: Age distribution of patients (n=285)

Age Ranges (in years)	Females	Males	Total	%
18-19	1	0	1	0.35
20-29	2	0	2	0.70
30-39	7	19	26	9.12
40-49	15	37	52	18.25
50-59	34	45	79	27.72
60-69	30	43	73	25.61
70-79	18	26	44	15.44
80-89	0	8	8	2.81
Total	**107**	**178**	**285**	**100**

The number of non-smokers n= 227 (79.65%) and non-alcoholics n= 204 (71.58%) were higher when compared to smokers and alcoholics. In comparison to female, males have higher numbers of alcoholics and smokers. The average in-patient hospital stay days was found to be 9.75 days. Majority of the patients were having hospital stay of 1-10 days i.e. 182 (63.86%) in which male were 113 (39.65 % of 285 patients) and female were 69 (24.21% of 285 patients) as in Table 2. Most common complaints for hospital admission were body & peripheral swelling followed by cough & expectoration. Out of 285 study population, Hypertension (53.68%) was found as major past medical condition compared to other diseases like Diabetes Mellitus (45.26%), IHD (12.63%) as in Figure 4. 60 patients were not having past medical history, in which males were 37 and females were 23.

Table 2: Distribution of patients based on in-patient stay days

In-patient stay range (days)	Male	Female	Total
1-10	113 (39.65%)	69 (24.21%)	182 (63.86%)
11-20	60 (21.05%)	36 (12.63%)	96 (33.68%)
21-30	3 (1.05%)	2 (0.70%)	5 (1.75%)
31-40	2 (0.70%)	0	2 (0.70%)
Total	**178 (62.46%)**	**107 (37.54%)**	**285 (100%)**

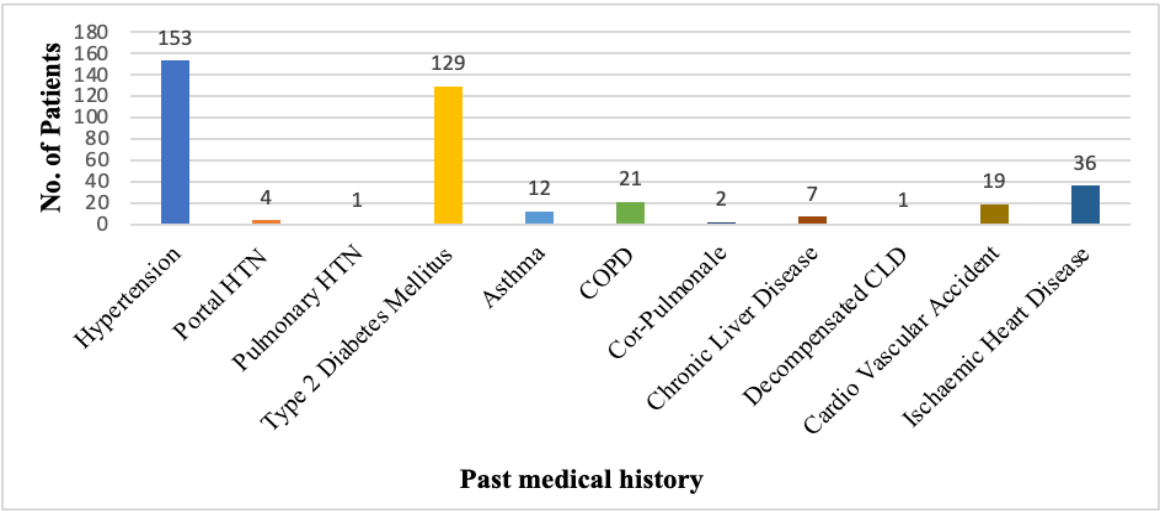

Fig 1: Distribution of patients based on past medical history

Table 3: contains various categories of Antihypertensive agents which were commonly prescribed during the study period.

Categories	Name of the drugs
ACE Inhibitors	Enalapril, Ramipril, Perindopril Erbumine
ß-Blocker	Atenolol, Propranolol, Bisoprolol
α + β Blocker	Labetalol, Carvedilol
Diuretics	Hydrochlorothiazide, Furosemide, Torasemide, Spironolactone, Chlorthalidone, Amiloride, Metolazone
CCBs	Amlodipine, Clinidipine
Angiotensin II receptor antagonist	Telmisartan, Losartan
Endothelin receptor antagonist	Ambrisentan
Central Sympatholytics	Clonidine
Vasodialators	Nitroglycerin, Isosorbide Dinitrate, Hydralazine

Tablets given through oral route 197 (68.64%) were commonly prescribed, followed by injections given through i.v route. On an average 3.81 antihypertensive agents were prescribed per patient in ward during the study period. In which patients being prescribed with at least 2 antihypertensive agents were higher in number (23.51%) as depicted in Figure 2.

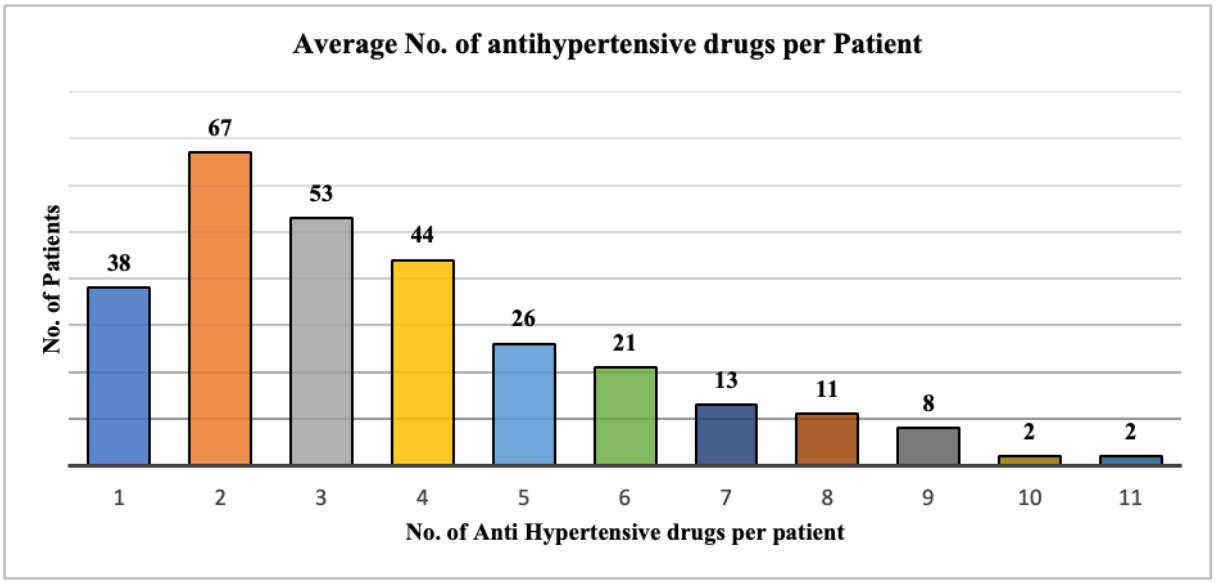

Fig 2: Average no. of anti-hypertensive drugs per patient

In single therapy, Furosemide had the highest number of units 1558 (20.65%) followed by Spironolactone 837.5 (11.10%). In dual therapy, Telmisartan + Hydrochlorothiazide had the highest number of units prescribed 75 (0.99%) as depicted in Table 4.

Table 4: Various drug therapies & units utilized for antihypertensive agents

Various drug therapy	Anti-hypertensive drug class	Name of the Drugs	Units	%
Single therapy	ACE Inhibitors	Ramipril	162	2.15
		Enalapril	5	0.07
		Perindopril Erbumine	42	0.56
	ß-Blocker	Propranolol	90	1.19
		Metoprolol	451.5	5.98
		Bisoprolol	31.5	0.42
		Atenolol	18	0.24
	α + β Blocker	Labetalol	3	0.04
		Carvedilol	160	2.12
	CCBs	Amlodipine	702	9.31
		Clinidipine	236	3.13
	Diuretics	Furosemide	1558	20.65
		Hydrochlorothiazide	45	0.60
		Torasemide	190.5	2.53
		Spironolactone	837.5	11.10
		Metolazone	17	0.23
		Chlorthalidone	20	0.27
		Amiloride	8	0.11
	Central Sympatholytics	Clonidine	51	0.68
	Endothelin receptor antagonist	Ambrisentan	24	0.32
	ARB	Telmisartan	652	8.64
		Losartan	38	0.50
	Vasodialators	Nitroglycerin	6	0.08
		Isosorbide Dinitrate	7	0.09
		Hydralazine	4.5	0.06
Total single therapy (A)			**7401.77**	**98.11**
Dual therapy	K Sparing Diuretics + Loop Diuretics	Torasemide + Spironolactone	41	0.54
	ACE Inhibitors + CCBs	Perindopril Erbumine + Amlodipine	8	0.11
	ARBs + Thiazide Diuretic	Telmisartan + Hydrocholorothiazide	75	0.99
		Losartan + Hydrocholorothiazide	11	0.15
	Anti-platelet + Dyslipidemic agent	Aspirin + Atorvastatin	3	0.04
	Vasodialator +	Isosorbide Dinitrate +	4.5	0.06

	Vasodialator	Hydralazine		
Total dual therapy (B)			**142.5**	**1.89**
Total units given (A+B)			**7544.27**	**100**

Among concomitant drugs Atorvastatin and aspirin were most commonly utilized.

The drugs were classified according to ATC classification. DDD & DDD/100 bed days were calculated using WHO recommended DDD [Table 6]. The highly utilized antihypertensive agent during the study period in general medicine ward was found to be Propranolol with 187.82 DDD/100 bed-days and its PDD:DDD was 1.74. Current study found that the total consumption of antihypertensive agents in the general medicine ward was 6807.40 DDD; and 890.75 in terms of DDD/100 bed days as shown in Table

Table 5: Antihypertensive drug consumption in terms of DDD & DDD/100 bed days

Anti-hypertensive drugs	Route	ATC code	WHO recommended DDD (mg)	Calculated DDD	DDD/100 bed days	PDD	PDD:DDD
Furosemide	O/P	C03CA01	40	1683.25	46.95	731.85	0.43
Spironolactone	O	C03DA01	75	386.33	88.04	314.95	0.82
Hydrochlorothiazide	O	C03AA03	25	76	29.35	20.65	0.27
Metolazone	O	C03BA08	5	17	5.87	0.92	0.05
Torasemide	O	C03CA04	15	275.5	17.61	44.92	0.16
Chlorthalidone	O	C03BA04	25	10	29.35	2.72	0.27
Amiloride	O	C03DB01	10	4	11.74	0.43	0.11
Telmisartan	O	C09CA07	40	714.63	46.95	310.71	0.43
Losartan	O	C09CA01	50	48.5	58.69	26.36	0.54
Propranolol	O	C07AA05	160	12.69	187.82	22.07	1.74
Atenolol	O	C07AB03	75	10.33	88.04	8.42	0.82
Bisoprolol	O	C07AB07	10	12.13	11.74	1.32	0.11

Metoprolol	O	C07AB02	150	99.5	176.08	162.23	1.63
Carvedilol	O	C07AG02	37.5	14.33	44.02	5.84	0.41
Labetalol	O/P	C07AG01	0.6	100	0.70	0.65	0.01
Clinidipine	O	C08CA14	10	292	11.74	31.74	0.11
Amlodipine	O	C08CA01	5	949	5.87	51.58	0.05
Ramipril	O	C09AA05	2.5	191.8	2.93	5.21	0.03
Enalapril	O/P	C09AA02	10	2.5	11.74	0.27	0.11
Perindopril Erbumine	O	C09AA04	4	44	4.70	1.91	0.04
Clonidine	O/P	C02AC01	0.45	11.33	0.53	0.06	0.00
Ambrisentan	O	C02KX02	7.5	160	8.80	13.04	0.08
Isosorbide Dinitrate	O	C01DA08	60	2.08	70.43	1.36	0.65
Hydralazine	O	C02DB02	0.1	1687.5	0.12	1.83	0.00
Nitroglycerin	O	C01DA02	5	3	5.87	0.16	0.05

Atorvastatin had the highest consumption 1523 DDD in general medicine ward as concomitant drugs as in Table 6.

Table 7: Concomitant drugs utilized along with anti-hypertensive agents

Concomitant drugs	Route	ATC code	WHO recommended DDD (mg)	Calculated DDD	DDD/1OO bed days
Aspirin	O	B01AC06	1 Tablet	983.27	1.17
Clopidogrel	O	B01AC04	75	27	88.03
Ticagrelor	O	B01AC24	0.18	9000	0.21
Rosuvastatin	O	C10AA07	10	80	11.74
Atorvastatin	O	C10AA05	20	1523	23.48

DISCUSSION & CONCLUSIONS

An observational study was performed for a period of three months in the inpatient department of the general medicine ward in ESIC MC-PGIMSR, which is a more than 500 bedded multi-speciality

teaching Hospital in Bengaluru. Now the study was conducted from June 2022 to August 2022. A total of 285 subjects were enrolled in the study based on various inclusion and exclusion criteria. The average age of the study subjects was found to be 56.64 ±12.88 years. In our study majority of the patients belongs to the age group of 50-59 years followed by 60-69 years which is 28% & 26% of the study population respectively. The course of the study was confirmed with one previous Indian study *Nachiya et al.*,(2015) on hypertensive subjects who reported the number of male subjects as 61.7% and female subjects as 38.3%. Another Indian study *Jainaf et al.*, (2014) revealed that hypertension was more prevalent in male subjects (51%) than female subjects (49%). The substance abuse in the study population was cigarettes smoking and alcohol. Substance abuse results have shown that the total number of smokers and alcohol addicts in the study population consists of 20% and 28% of the population respectively. The smoking addict population comprises 100% (58) males. In the study population, no smoking habits or history were found in the female population. The same pattern can be seen in alcohol addicts in which the majority of the addicts are male (80) and number of female addict was 1. From the above data, it can be said that cigarette smoking, alcohol or unhealthy habits play an important role in increasing the risk of hypertension. This statement agreed with a previous Indian study *Jainaf et al.*,(2014).

Nachiya et al., (2015) study revealed that 201 hypertensive subjects had been prescribed 10,638 units of antihypertensive drugs over a period of 1 year, and the ACE I drug class was the most frequently prescribed antihypertensive drug among others. On accountability of overall drug prescribing pattern of this present study, 285 patients had very high usage than that reported by Nachiya et al. in 2015; considering in this study 285 patients had a consumption of 7544.27 units of antihypertensive agents over a period of 3 months. Diuretics are the most prescribed antihypertensive comprising of 35.47% of the total units of antihypertensive agents followed by CCBs (12.43%). Furosemide has the highest units consumed i.e 1558 which comprises 20.65% of total antihypertensive units prescribed, followed by spironolactone 837.5 (11.10%), amlodipine 702 (9.31%), Telmisartan 652 (8.64%). Apart from traditional antihypertensives, there are other classes of drugs which have been prescribed having a secondary effect in reducing BP, such as aspirin 890.27 units (11.80%), and Atorvastatin 1059 units (14.04%).

Mono therapy was more frequently used than combination therapy (98.11% vs 1.89%) and the very least prescribed drugs were as follows perindopril erbumine + amlodipine 8 (0.10%), nitroglycerine 6 (0.08%), isosorbide dinitrate + hydralazine 4.5 (0.06%). The total consumption of antihypertensive drug in the General medicine ward was measured in DDD/100 bed-days. Propranolol was found to have high utilization in the General medicine ward having 187.82 DDD/100 bed days than other drugs analysed in the study, which means 187.82% of in-patients were receiving 1 DDD of Propranolol on average daily. Atenolol and spironolactone having 88.04 DDD/100 bed days. The current study found that total antihypertensive drug consumption in the General medicine ward was 890.75 DDD/100 bed days. When the PDD:DDD ratio is less then 1, it indicates underutilisation, and when it is greater than 1, it indicates over utilisation of medication. Our current study found that ß-blockers like Propranolol and Metoprolol were over-utilized with PDD:DDD ratio of 1.74 & 1.63, indicating potential overuse of the drugs. Along with Antihypertensives concomitant drugs were also given to patients in which Clopidogrel and Atorvastatin were most commonly given with a DDD/100 bed days of 88.03 and 23.48 respectively.

The only drawback of this study is that it was carried out only for a short period of time. The data collected may not be an appropriate representation of the population as it was of a single ward of the hospital. A cost analysis study can be carried out.

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