Original Research Article

A cost variation analysis of the antihypertensives: The need for essential of medicines list to fit the bill

Sharmila Sinha[1], Tejus A[2*]

[1]Command Hospital, Lucknow, Uttar Pradesh, INDIA.
[2]Department of Pharmacology, Army College of Medical Sciences, Delhi Cantt, INDIA.
Email: ddmtejus@gmail.com

Abstract

Background: Hypertension is a chronic disorder posing important public health problems and a risk for cardiovascular & other complications. Various guidelines have been framed from time to time to define various grades of hypertension and its management including pharmacotherapy. To follow the principle of rational drug therapy the 20th Essential medicines list (2017) by the World Health Organisation and National List of essential medicines, India (2015) include antihypertensives, but the differences in two lists with respect to medicines included in the list and their cost variation is seldom studied. **Objectives:** To compare the antihypertensives included in the 20th Essential medicines list (EML) and National List of essential medicines (NLEM). To do a cost variation analysis amongst antihypertensives selected in each of the first line antihypertensive groups. **Methodology:** The antihypertensive medicines included in EML and NLEM was classified and differences in the lists were brought out. The percentage cost variation and cost ratio between the medicines in both the lists were tabulated. **Results:** Enalapril was the preferred Angiotensin Convertase Enzyme inhibitor, but NLEM also includes Ramipril. Amongst the Angiotensin Receptor Blockers Losartan was preferred by EML but NLEM prefers Telmisartan. The maximum percentage cost variation and maximum cost ratio was exhibited by Ramipril 5mg, Telmisartan 40 mg, Amlodipine 10mg and hydrochlorothiazide 12.5mg. **Conclusion:** The antihypertensive are always included in NLEM and EML after great deliberation by experts, but still cost variation exists amongst the same. Hence, regulators must device mechanisms to strictly regulate the prices of these medicines.

Key Words: Antihypertensives, Essential medicines list, National List of essential medicines, Cost variation

***Address for Correspondence:**
Dr. Tejus A, Department of Pharmacology, Army College of Medical Sciences, Delhi Cantt, INDIA.
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INTRODUCTION

Hypertension is an important risk factor for cardiovascular and renal disease and is defined by the American College of Cardiology/American Heart Association 2017 guidelines as systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 80 mmHg.[1,2] This is in variation to widely practiced JNC 7 guidelines which had placed individuals with systolic blood pressure 120-139 mmHg and diastolic blood pressure between 80-90 mmHg as pre-hypertension and the cut-off blood pressure for classifying an individual as hypertensive was 140/90 mmHg.[1,2] This new definition significantly adds to the burden of disease with an increase in prevalence of hypertension in United states adults to 46% in comparison to 32% with JNC 7 guidelines.[1-3] The new guidelines adds great emphasis on the accurate measurement of Blood Pressure and detection of secondary hypertension. Non Pharmacological measures like increasing physical activity, loss of weight, dietary pattern, restricted alcohol and salt intake with supplementation of potassium takes centre stage in the management of stage 1 hypertension (≥ 130-139/ 80-89

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mmHg). [3, 4]Pharmacotherapy is added to stage 1 hypertension individuals with 10 year cardiovascular risk > 10% or those manifesting with complications like stroke, coronary heart disease and congestive heart failure. Pharmacotherapy is recommended for all patients of stage 2 hypertension (≥ 140/90 mmHg).[4-6]The first line antihypertensives as per guidelines are Angiotensin Convertase Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blocker (ARBs), Calcium Channel Blockers (CCBs) and diuretics. All these groups are considered first line based on the trials demonstrating significant reduction in cardiovascular risk.[4-6] Beta blockers which were one of the first line drugs in JNC 7 guidelines no longer enjoy the status, as they demonstrate no significant benefit in preventing the mortality or complications from hypertension.[7] World Health Organisation (WHO) has enlisted socio-economic factors including cost of treatment, low levels of literacy and cognition, lack of social support framework, polypharmacy, adverse drug reactions to negatively influence the compliance to treatment.[8-11]In a developing country like India with a lack of central health insurance schemes approximately 52% of the health expenditure is met through the pockets of patients or their relatives.[8] Medicines contribute to major part of health expense and WHO report states that upto 5% of the expenditure can be avoided by practicing rational use of medicines, maintaining the quality and avoiding overpricing.[8]Essential drugs as defined by WHO are those medicines that satisfy the priority healthcare needs of majority of population. They are selected after giving due regards to relevance in public health, efficacy, safety and cost-effectiveness.[8, 9]This concept of essential drugs plays a vital role in promoting rational use of medicines. In order to help its member countries, WHO published a first model list of essential medicines (EML) in 1977, which has been revised every two years to the current 20th EML published in 2017. Similar to EML each member nation have developed its own list, India ventured into the arena with its first National list of essential medicines (NLEM) in 1996, revised from time to time with the latest NLEM published in 2015.[9-11]NLEM 2015 published by Ministry of Health and Family welfare, Government of India contains 376 medicines and 24 Fixed dose combinations, which were included after due deliberation and few glaring gaps left in NLEM 2011. [12, 13]As the prices of medicines play a crucial role in determining compliance to treatment, prescribing drugs from NLEM or EML is an important measure to put a check on indiscriminate prescription of medicines by treating physicians. Studies have suggested that physicians often have poor knowledge regarding the prices of medicines offered by pharmaceuticals.[14, 15] Study suggests that most EML drugs are being sold in UK and South Africa at a cost significantly higher than the production costs. Hence even if medicines are prescribed from NLEM/ EML, if generic prescription is not followed then there is still chance of burdening the patient with a costlier brand. Hence, this study was conceptualized to compare the antihypertensives included in EML and NLEM and to do a cost variation analysis on the same. This is important to understand the similarity and differences in selection of antihypertensives in both the list, as it provides ample scope to determine future possible modifications in NLEM. It also will motivate physicians to be more careful while prescribing medicines and prefer Non-proprietary name over proprietary name of the medicines.

AIMS AND OBJECTIVES

1. To compare the antihypertensives included in the 20th WHO-EML and NLEM 2015.
2. To do a cost variation analysis amongst antihypertensives selected in each of the first line antihypertensive groups.

METHODOLOGY

The antihypertensive medicines in EML (i.e. those antihypertensives enlisted in 20th WHO-EML, 2017) and NLEM (i.e. those antihypertensives enlisted in NLEM, 2015) were classified group wise into ACEIs, ARBs, CCBs, diuretics and others (i.e. antihypertensive not belonging to any of the earlier mentioned groups).[16, 17] A comparison of antihypertensives included in EML and NLEM was noted group wise. Current Index of Medical Specialties (CIMS) Jan to Apr 2019 edition, Online Current Index of Medical Specialties (CIMS) India database and Drug today (Jan-Mar 2019 edition) was used to find the price of various first line antihypertensive (ACEIs, ARBs, CCBs and diuretics) brands enlisted in EML and NLEM. All prices were recorded in INR. The brand with minimum and maximum cost for a particular dose was recorded. The percentage cost variation of the antihypertensive formulation selected in each group was calculated based on the formula as mentioned below: Percentage cost variation = (Maximum cost of the brand - Minimum cost of the brand) / Minimum cost of the brand x 100.[8, 9] Cost ratio is the ratio of the most expensive brand of antihypertensive to the least expensive brand. It is calculated within each group of antihypertensives to represent the number of times the costliest brand of a particular formulation will cost more in comparison to the cheapest brand of the same formulation.[8, 9] For comparison between the NLEM and EML, Cost ratio infers to the ratio of cost of costliest brand of antihypertensive in NLEM group to that of cheapest brand in EML group. This represents the number of times

the costliest antihypertensive in NLEM group will cost more in comparison to the cheapest antihypertensive in EML group. [8, 9]The data collected was tabulated in windows Microsoft Excel and was analysed for percentage cost variation, cost ratio within each formulation of the group and between NLEM and EML groups. The results were tabulated.

RESULTS

Enalapril and Ramipril were included amongst the group of ACEIs in NLEM, whereas only enalapril was considered by EML. The salt of enalapril was specified only by EML as hydrogen Maleate, whereas NLEM was silent on the same. Doses of 2.5 and 5 mg of enalapril were included in both EML and NLEM. In NLEM along with enalapril, 2.5 and 5 mg dose of Ramipril were also included. [Table 1]In EML Losartan was preferred as the angiotensin receptor blocker (ARB), including doses of 25, 50 and 100 mg in the list. NLEM preferred Telmisartan as the ARB, including doses of 20, 40 and 80 mg. [Table 1] Both EML and NLEM preferred amlodipine as the calcium channel blocker of choice. In EML dose of only 5 mg of amlodipine is preferred where as in NLEM doses of 2.5 mg, 5 mg and 10 mg find its place. EML again specifies the preferred salt of amlodipine as Maleate, Mesylate or Besylate, whereas NLEM remains silent on the issue. [Table 1] Hydrochlorothiazide remains the preferred diuretic by both EML and NLEM. EML has included both liquid dosage form (50 mg/5 ml) and solid dosage form (12.5 and 25 mg tablets) in the list whereas NLEM only includes the solid dosage form. [Table 1] Beta-blockers although relegated as a last line antihypertensive by the American College of Cardiology/American Heart Association 2017 guidelines, it still finds its place in both EML and NLEM. In EML, Bisoprolol (1.25 and 5 mg) is the preferred beta-blocker with alternatives as atenolol, Metoprolol and carvedilol. In NLEM, Atenolol (50 and 100 mg) is still the preferred beta-blocker. EML clearly cautions not to use atenolol in individuals more than 60 years, but no such remarks in NLEM. Inj Labetolol 5 mg/ml is included in NLEM for management of hypertensive emergency. Both NLEM and EML prefer methyldopa for pregnancy induced hypertension, with EML also including hydralazine for the same indication. The vasodilator sodium nitroprusside is included by both NLEM and EML for management of hypertensive emergency. [Table 1] The maximum percentage cost variation and maximum cost ratio was exhibited by Ramipril 5 mg (ACEIs), Telmisartan 40 mg (ARBs), Amlodipine 10 mg (CCBs) and hydrochlorothiazide 12.5 mg (Diuretics). Angiotensin Convertase Enzyme Inhibitor (ACEI) included in NLEM (Ramipril) demonstrates greater percentage cost variation in comparison to ACEI included in ELM (Enalapril). In similar lines, Angiotensin receptor blocker (ARB) selected in NLEM (Telmisartan) exhibits greater percentage cost variation in comparison to ARB selected in ELM (Losartan). Calcium channel blocker (CCB) selected in NLEM and EML (Amlodipine) is same except for the dose, but one of the doses selected in NLEM (Amlodipine 10 mg) demonstrates greater percentage cost variation and cost ratio in comparison to the only dose included in EML (Amlodipine 5 mg). [Table 2, Table 3].The cost ratio between NLEM and EML antihypertensive groups demonstrates that the costliest ACEI in NLEM costs 18 times more than the cheapest ACEI in EML. Similarly the costliest ARB in NLEM costs 12 times more than the cheapest brand of ARB in EML. There is no cost variation in CCBs and diuretics as the choice of CCB and diuretics remain the same in both NLEM and EML. [Table 3]

Table 1: group wise comparative chart of antihypertensives included in eml and nlem

S.No	Anti-Hypertensive drug group	NLEM	EML
1.	Angiotensin Convertase Enzyme Inhibitors (ACEIs)	Enalapril Tablet 2.5 mg and 5 mg Ramipril Tablet 2.5 mg and 5 mg	Enalapril 2.5 mg; 5 mg (as hydrogen Maleate)
2.	Angiotensin Receptor Blocker (ARBs)	Telmisartan Tablet 20 mg, 40 mg and 80 mg	Losartan Tablet: 25 mg; 50 mg; 100 mg
3.	Calcium Channel Blockers (CCBs)	Amlodipine Tablet 2.5 mg, 5 mg and 10 mg	Amlodipine 5 mg (as Maleate, Mesylate or Besylate)
4.	Diuretics	Hydrochlorothiazide Tablet 12.5 mg and 25 mg	Hydrochlorothiazide Oral liquid: 50 mg/5 mL. Solid oral dosage form: 12.5 mg; 25 mg
5.	Beta Blockers	Atenolol Tablet 50 mg Tablet 100 mg Labetalol Injection 5 mg/ml	Bisoprolol 1.25 mg; 5 mg (Includes atenolol, metoprolol and carvedilol as alternatives. Atenolol should not be used as a first-line agent in uncomplicated hypertension in patients >60 years).

6.	Others	Methyldopa Tablet 250 mg Tablet 500 mg	Methyldopa (It is listed for use only in the management of pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines). Tablet: 250 mg
		Sodium nitroprusside Injection 10 mg/ml	Sodium nitroprusside Powder for infusion: 50 mg in ampoule Hydralazine (It is listed for use only in the acute management of severe pregnancy-induced hypertension. Its use in the treatment of essential hypertension is not recommended in view of the evidence of greater efficacy and safety of other medicines) Powder for injection: 20 mg (hydrochloride) in ampoule. Tablet: 25 mg; 50 mg (hydrochloride).

Table 2: cost variation analysis of various brands of first line antihypertensives included in eml and nlem.

S.No	Anti-Hypertensive drug group	Total No. of brands available	Cost in INR Minimum cost (per 10 tab)	Percentage cost variation Maximum cost (per 10 tab)	Price range (per 10 tab)	
1.	Angiotensin Convertase Enzyme Inhibitors (ACEIs)					
	Tab Enalapril 2.5 mg	20	6.00	18.69	6.00-18.69	211.50
	Tab Enalapril 5 mg	22	9.00	32.00	9.00-32.00	255.56
	Tab Ramipril 2.5 mg	31	21.00	75.00	21.00-75.00	257.14
	Tab Ramipril 5 mg	30	27.00	111.06	27.00-111.06	311.33
2.	Angiotensin Receptor Blocker (ARBs)					
	Tab Telmisartan 20 mg	20	12.00	45.00	12.00-45.00	275.00
	Tab Telmisartan 40 mg	51	15.00	85.10	15.00-85.10	467.33
	Tab Telmisartan 80 mg	09	25.50	120.00	25.50-120.00	370.58
	Tab Losartan 25 mg	26	10.00	38.00	10.00-38.00	280.00
	Tab Losartan 50 mg	33	19.00	61.70	19.00-61.70	224.73
	Tab Losartan 100 mg	02	91.00	113.00	91.00-113.00	24.17
3.	Calcium Channel Blockers (CCBs)					
	Tab Amlodipine 2.5 mg	24	4.50	27.00	4.50-27.00	500.00
	Tab Amlodipine 5 mg	56	13.26	66.67	13.26-66.67	402.79
	Tab Amlodipine 10 mg	28	12.00	127.50	12.00-127.50	962.50
4.	Diuretics					
	Tab Hydrochlorothiazide 12.5 mg	4	7.61	9.55	7.61-9.55	25.49
	Tab Hydrochlorothiazide 25 mg	2	13.94	14.70	13.94-14.70	5.45

Table 3: cost ratio of various brands of first line antihypertensives included in eml and nlem.

S.No	Anti-Hypertensive drug group	Total No. of brands available	Cost in INR Minimum cost (per 10 tab)	Maximum cost (per 10 tab)	Price range (per 10 tab)	Cost Ratio	Cost Ratio (NLEM vs EML)
1.	Angiotensin Convertase Enzyme Inhibitors (ACEIs)						
	Tab Enalapril 2.5 mg	20	6.00	18.69	6.00-18.69	3.115	18.51
	Tab Enalapril 5 mg	22	9.00	32.00	9.00-32.00	3.555	
	Tab Ramipril 2.5 mg	31	21.00	75.00	21.00-75.00	3.571	
	Tab Ramipril 5 mg	30	27.00	111.06	27.00-111.06	4.113	

2.	Angiotensin Receptor Blocker (ARBs)						
	Tab Telmisartan 20 mg	20	12.00	45.00	12.00-45.00	3.75	12.00
	Tab Telmisartan 40 mg	51	15.00	85.10	15.00-85.10	5.673	
	Tab Telmisartan 80 mg	09	25.50	120.00	25.50-120.00	4.705	
	Tab Losartan 25 mg	26	10.00	38.00	10.00-38.00	3.80	
	Tab Losartan 50 mg	33	19.00	61.70	19.00-61.70	3.247	
	Tab Losartan 100 mg	02	91.00	113.00	91.00-113.00	1.241	
3.	Calcium Channel Blockers (CCBs)						
	Tab Amlodipine 2.5 mg	24	4.50	27.00	4.50-27.00	6.00	-
	Tab Amlodipine 5 mg	56	13.26	66.67	13.26-66.67	5.027	
	Tab Amlodipine 10 mg	28	12.00	127.50	12.00-127.50	10.625	
4.	Diuretics						
	Tab Hydrochlorothiazide 12.5 mg	4	7.61	9.55	7.61-9.55	1.254	-
	Tab Hydrochlorothiazide 25 mg	2	13.94	14.70	13.94-14.70	1.054	

DISCUSSION

Hypertension is a chronic medical condition needing lifelong treatment with medications in most of the cases. In a developing country like India this added financial burden greatly affects compliance to treatment. In order to promote rational drug therapy prescribing from NLEM/EML is warranted. Most of the drugs included in NLEM and EML are non-proprietary by nature but still huge variation exists in the various brands available in the market. Hence to compare both EML and NLEM with respect to antihypertensives included, this study was postulated. Enalapril is the preferred ACEI in both NLEM and EML. Chang CH, et al (2015) in their study on different ACEIs and their association with overall and cause specific mortalities amongst hypertensive individuals concluded that enalapril and fosinopril carried a modest increase in risk in comparison to ramipril, lisinopril, perindopril and imidapril.[19] But the mortality risk difference between individual ACEIs are marginal and carry limited significance clinically.[19]Hence the additional inclusion of ramipril in NLEM and probably will find its place in EML in future. Telmisartan was the preferred ARB in NLEM whereas Losartan was preferred in EML. Kalikar M, et al (2017) in their randomized open label study to determine efficacy and tolerability of ARBs (Olmesartan, Telmisartan and Losartan) in stage 1 hypertensives concluded that for reducing systolic blood pressure Olmesartan appears more efficacious in comparison to others and for reducing diastolic blood pressure Olmesartan and Telmisartan are more efficacious in comparison to Losartan. The most favorable effects on fasting blood glucose and lipid profile was exhibited by Telmisartan. [20] In a contrasting review article on different therapeutic choices with ARBs, Losartan was suggested to be the first choice for hypertensives at high risk of stroke. Both Telmisartan and Losartan were considered ideal for those with high cardiovascular risk.[21] Telmisartan benefits proteinuria the most and Losartan is the ARB of choice for diabetic nephropathy.[21] Olmesartan use should be cautious in individuals with diabetes mellitus with chronic kidney disorders, as studies suggest an increased cardiovascular risk in this subgroup of individuals.[21]Hence the selection of ARBs into NLEM/EML needs further studies. Amlodipine remains the calcium channel blocker of choice in both EML and NLEM as it demonstrates good efficacy and safety. In addition large randomized controlled trials have demonstrated significant cardiovascular event reduction with amlodipine.[22] Diuretics are one of the first line antihypertensives and hydrochlorothiazide is the diuretic of choice in both NLEM and EML. The availability of newer more efficacious antihypertensives have relegated diuretics as one of the alternative first line antihypertensive.[23, 24]Although hydrochlorothiazide find its place in the list, evidence support its inferiority to other thiazide like diuretics (Chlorthalidone and Indapamide) with regards to duration of action and prevention of cardiovascular events.[23, 24] Indapamide is more efficacious to improve albuminuria in diabetics, reducing left ventricular mass Index, reducing oxidative stress , inhibiting platelet aggregation and moreover does not carry adverse effects profile on glucose and lipid metabolism.[23] The only reason for hydrochlorothiazide to appear in the list appears to be its cost and availability.[23] Hence future EML and NLEM must consider replacing it with better alternatives. Beta-blocker included in NLEM is atenolol whereas EML prefers Bisoprolol. Numerous trials have indicated against the use of atenolol as the first line antihypertensives and the JNC-8 and American College of Cardiology/American Heart Association 2017 guidelines clearly relegate beta-blockers as last line antihypertensives.[2, 24, 25]Trials suggest carvedilol to provide greater reduction in cardiovascular morbidity and mortality with lesser adverse effects on lipid profile and blood sugar.[26]Hence more precautionary note to be placed

in NLEM in future revisions. In our study the percentage cost variation of ACEI Enalapril 2.5 mg is 211.50% and enalapril 5 mg is 255.50%. These results surpass the variation in earlier study by Nair MK et al (2017) where the percentage cost variation of enalapril 2.5 mg was 156.82% and enalapril 5 mg was 145.6%.[27] Similarly the percentage cost variation of other antihypertensives Ramipril 2.5 mg 257.14% (Vs 115.52%), Ramipril 5 mg 311.33% (Vs 169.35%), Losartan 25 mg 280% (Vs 241.67%), Telmisartan 40 mg 467.33% (Vs 207.5%) and Telmisartan 80 mg 370.58% (Vs 50.562%) clearly exceeds the variation seen in earlier study by Nair MK et al (2017). [27] However, the percentage cost variation of Losartan 50 mg 224.73% (Vs 241.67%) and Telmisartan 20 mg 275% (Vs 322.22) were lesser in our study in comparison to the earlier study by Nair MK et al (2017). [27]The percentage cost variation of CCB in our study for amlodipine 2.5 mg 500% and amlodipine 5 mg 402.79% is clearly lesser than the cost variation results by Kamath L, et al (2017) who projected a percentage cost variation of 1040.58% for amlodipine 2.5 mg and 670.58% for amlodipine 5 mg.[28]Similarly the percentage cost variation in our study for hydrochlorothiazide 12.5 mg 25.49% (Vs 58.83%) and hydrochlorothiazide 25 mg 5.45% (Vs 50.09%) is clearly lesser than the results by Kamath L, et al (2017).[27]In line with study of Kamath L, et al (2017) amlodipine 10 mg exhibits the maximum percentage cost variation and cost ratio.[28]

CONCLUSION

In this era of explosion of pharmaceutical formulations with physicians lacking the knowledge of price of most formulations, it is very much essential for the authorities to keep a stringent check on the cost of medicines. The NPPA (National Pharmaceuticals Pricing Authority) under the aegis of Ministry of Chemical and Fertilizers, Government of India has published the Drugs (Price Control) Order, 2013 which restricts the price and should discourage the undue profit making by the pharmaceutical companies. Still the existing variation clearly highlights the need for regulatory authorities to question the pharmaceutical companies, further tighten the price of medicines enlisted in NLEM and physicians to adhere to the nonproprietary name prescription. These steps will greatly benefit and reduce the economic burden on the clientele of our healthcare services.

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