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Pharmacist Role In Drug Efficacy & Safety Implementation On FDC; A Pilot Study

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ABSTRACT

Most of the patients in current scenario are treated with more than one anti-hypertensives and most often with fixed dose combinations. Hence the use and efficacy of fixed dose combination are controversial and is the most debated issue in Indian perspective The aim of this randomized pilot study was to evaluate the rationality and side effect profile of fixed dose anti-hypertensive combinations used in our hospital. A total of 25 hypertensive patients prescribed with anti-hypertensive FDCs were randomly selected and their outpatient record were monitored and recorded for a period of 2 weeks. The data was then suitably analyzed. Out of the 13 FDCs, only one FDC (7.69%) have its APIs present in both EML of WHO and NLEM of India. There was no established evidence in terms of therapeutic efficacy and safety for the 3 combinations (23.07%).76.92% of FDCs were cost effective when compared with their individual components. 11 FDCs (84.61%) provide published literature on the reduction of either dose of individual drugs or their adverse effects. Only one FDC was found to be irrational in this study. Giddiness (33.33%) was the most frequently seen side effect among the prescribed FDCs. During this limited study period with only 13 anti-hypertensive FDCs, we were able to find an irrational FDC, which clearly show an urgent need to conduct further studies on evaluating the rationality of FDCs as a whole. As a clinical pharmacist, our immense role in evaluating the rationality of FDCs could enable the DCGI to withdraw irrational FDCs from the market.

Keywords: Hypertension, Fixed dose combination, Rationality, Side effects, Clinical pharmacist.

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INTRODUCTION

The ultimate public health goal of antihypertensive therapy is the reduction of cardiovascular and renal morbidity and mortality[1]. Drug selection in an individual is mainly based on his age and co-morbid conditions. Although it is occasionally possible to identify a specific cause for hypertension in some patients, BP elevation is usually multifactorial, making it very difficult, to normalize pressure by only a single pressor mechanism[2]. Addition of a second drug from a different class should be initiated when use of a single drug in adequate doses fails to achieve the BP goal. When BP is more than 20/10 mmHg above goal, consideration should be given for initiating therapy with two drugs, either as separate prescriptions or in fixed-dose combinations[1]. Hence the importance of fixed dose combination came into view.

JNC 8 recommends selection from the following four specific medication classes:

- Angiotensin- converting enzyme(ACE) inhibitors
- Angiotensin-receptor blockers
- Calcium-channel blockers
- Diuretics

Due to an ever increasing use of antihypertensive fixed dose combinations, there are several debates regarding this issue. As two sides of a coin, FDC's are both merited and demerited.

Some of the merits offered by them include;

- Simpler dosage schedule improves compliance and therefore improves treatment outcomes[4.]
- Reduced in advertent medication errors[4].
- More convenience in prescribing[3].
- Combination therapies with agents having complementary mechanism of action may provide advantages of each type of agent and reduce some of the adverse effects of high dose of individual drug[5].
- Blood pressure targets will be attained more quickly[6.]
- Reduced pill burden[3].

The market for hypertensives is expected to slow down due to patent expiries of major anti-hypertensive drugs. The only barrier to the global anti- hypertensive's market is the recent and upcoming patent expiries of drugs. However, the expected launch of novel molecules with disease modifying characteristics and better safety and efficacy will drive the market in the forecast period.[10]

However, the market is expected to rise slightly after 2015 due to increased usage of fixed dose combinations and the increase in prescription population on generics. [10]

MATERIALS AND METHOD

In the pilot trail, the data of 25 patients were collected randomly for a period of 2 weeks. The trail included all outpatients (both gender) attending the cardiology department of age ≥ 18 years. The main end point of the trial include the patients below 18 years, with incomplete medical records & those who were not willing to participate in the study. The study also excluded pregnant and breast feeding women.

Based on inclusion and exclusion criteria 25 prescriptions issued during the period of2 weeks were randomly collected and the relevant data was analyzed and tabulated in a specially designed data collection form. Patient's demographic details, pertinent laboratory and clinical information were collected during the outpatient hours and by reviewing the medical records.

A comprehensive seven-point criterion developed by Panda et al was used for the evaluation of rationality of the FDCs. These criteria include all the dimensions of defining a rational FDC and appropriate weighting (score) has been attached to each criterion. Each FDC was assessed for number of active pharmacological ingredients, approval by regulatory authority, listing in WHO Essential Medicine List (EML) or National List of Essential Medicine (NLEM). The maximum scoring of seven point criteria is 14 with each criterion carrying a score of 2 and score ≥8 is considered rational.

The side effect of anti-hypertensive FDCs was monitored and noted during outpatient (OP) hours. Those newly diagnosed patients were followed up as possible.

RESULTS AND DISCUSSION

During the study period about 25 prescriptions containing anti-hypertensive FDCs were analyzed. Majority of patients were in the age group of 60-69 years (48%) as shown in figure 1. About 56% of the study populations were males and about 44% were females as shown in figure 2. Duration of hypertension in the study population is illustrated in figure 3. Their major comorbidities included diabetes (52%), CAD (48%), dyslipidemia (44%) and thyroid disorder (8%) as shown in figure 4.

There were 13 different anti-hypertensive FDCs prescribed as shown in table 1. Most commonly prescribed FDCs were found to be Olmesartan/HCTZ and Telmisartan/Amlodipine each with 16% as shown in figure 5.

Giddiness (33.33%) was the most frequently seen side effect among the prescribed FDCs. Hyperkalemia, cough, pedal edema, bradycardia, vertigo, and hypotension were the other side

effects observed with each representing 11.11%. The distribution of samples according to side effects of anti-hypertensive FDCs prescribed is illustrated in table.2.

Table 1: List of antihypertensive FDCs in the study:

Antihypertensive fixed dose combinations	Brand names	Strengths
Olmesartan + Amlodipine	OLMEZEST AM	20mg/5mg 40mg/5mg
Olmesartan + Amlodipine + HCTZ	TRIOLMEZEST	20mg/12.5mg/5mg 40mg/12.5mg/5mg
Olmesartan + HCTZ	OLMEZEST H	20mg/12.5mg 40mg/12.5mg
Bisoprolol + Amlodipine	CONCOR AM	5mg/2.5mg 5mg/5mg
Nebivolol + S-Amlodipine	NEBICARD SM	5mg/2.5mg
Amlodipine + Atenolol	AMLODAC AT	5mg/50mg
Telmisartan + Cilnidipine	ERITEL LN	40mg/10mg 80mg/10mg
Telmisartan + HCTZ	TELMIGET H	40mg/12.5mg 80mg/12.5mg
Telmisartan + Amlodipine	TELMIGET AM	40mg/5mg 80mg/5mg
Olmesartan + Metoprolol	OLMEZEST BETA	20mg/25mg
Losartan + Amlodipine	AMLOKIND L	50mg/5mg
Ramipril + Amlodipine	CARDACE AM	2.5mg/5mg 5mg/5mg
Ramipril + Metoprolol	CARDACE METO	2.5mg/25mg 5mg/50mg

Table 2: Distribution of the sample according to side effect for FDCs

Side effect for FDCs		No of prescriptions	Percent
Olmesartan + Amlodipine	Absent	3	75.0
	Giddiness	1	25.0
Olemsartan + Amlodipine + HCTZ	Absent	1	50.0
	Giddiness	1	50.0
Olmesartan + HCTZ	Absent	3	75.0
	Hyperkalemia	1	25.0
Ramipril + Metoprolol	Absent	0	0.0
	Cough	1	100.0
Bisoprolol + Amlodipine	Absent	2	66.7
	Pedal edema	1	33.3
Nebivolol + S-Amlodipine	Absent	1	50.0
	Bradycardia	1	50.0
Amlodipine + Atenolol	Absent	1	33.3
	Vertigo	1	33.3
	Giddiness	1	33.3
Telmisartan + Cilnidipine	Absent	1	100.0
	Hypotension	0	0.0
Telmisartan + HCTZ	Absent	3	100.0

	Hypotension	0	0.0
Telmisartan + Amlodipine	Absent	3	75.0
	Hypotension	1	25.0
Olmesartan + Metoprolol	Absent	1	100.0
	Hypotension	0	0.0
Losartan + Amlodipine	Absent	1	100.0
	Hypotension	0	0.0
Ramipril + Amlodipine	Absent	1	100.0
	Hypotension	0	0.0

Table 3: Interaction of APIs of FDCs:

Si no	Drugs	Effect	Severity	Type	Unfavourable/ Favourable
1.	Bisoprolol + Amlodipine	Hypotension and/or bradycardia	Moderate	Pharmacodynamic	Unfavourable
2.	Amlodipine+ Atenolol	Hypotension and/or bradycardia	Moderate	Pharmacodynamic	Unfavourable
3.	Nebivolol + Amlodipine	Hypotension and/or bradycardia	Moderate	Pharmacodynamic	Unfavourable

Table 4: Scoring by criteria:

SI.NO	1	2	3	4	5	6	7	8	9	10	11	12	13
FDC	OLS+ AML	OLS+ AML+ HCTZ	OLS+ HCTZ	BSL+ AML	NBV+ SAML	AML+ ATN	TLS+ CLN	TLS + HCTZ	TLS +AML	OLS + MTP	LSN + AML	RML + AML	RML + MTP
Total Score	13	11	13	11	6	8	12	11	13	11	13	11	11

OLS-Olmesartan; AML- Amlodipine; HCTZ- Hydrochlorothiazide; BSL- Bisoprolol; NBV- Nebivolol;

SAML- S- amlodipine; ATN- Atenolol; TLS- Telmisartan; CLN- Cilnidipine; MTP- Metoprolol; LSN- Losartan; RML-Ramipril.

The rationality of FDCs were studied and analyzed. The evaluation of results showed 7.69% of individual components of FDCs were present in both EML of WHO and NLEM of India, 76.92% contained at least one component in either EML of WHO or NLEM of India or both, and 15.38% of FDCs were not present in both the list.

The dose and proportion of each API present in FDCs (100%) was found to be appropriate for the individual use. Among the FDCs 76.9% of combinations possess the advantage of efficacy and safety over individual drugs administered separately based on established evidences. There was no established evidence in terms of therapeutic efficacy and safety for the 3 combinations such as Amlodipine/Atenolol, Metoprolol/Olmesartan, Nebivolol/S-amlodipine.

76.92% of FDCs were cost effective when compared with their individual components except Telmisartan/HCTZ, Ramipril/Metoprolol, and Ramipril/Amlodipine which cost more than the

individual components. 11 FDCs (84.61%) provide published literature on the reduction of either dose of individual drugs or their adverse effects. 76.9% FDCs had no unfavourable pharmacokinetic or pharmacodynamic interaction between APIs. Table 3 shows the list of interactions of APIs of FDCs.

The combination of olmesartan and amlodipine have established evidence of efficacy and safety over single compounds administered separately. This combination is preferred because of fully additive BP reduction, as calcium channel blockers are potent vasodilators ,may induce reflex activation of sympathetic nervous system and an increase in plasma rennin activity and thus angiotensin II production. This will potentiate the action of angiotensin II receptor blockers. Additionally combinations have been reported to have fewer side effects than each individual medication.

The triple drug combination of olmesartan + amlodipine + hydrochlorothiazide is found to be more efficacious and safe in reducing the high blood pressure in comparison with monotherapy or a combination of two drugs (namely olmesartan+ hydrochlorothiazide) of similar dose. Their efficacy was even extended to patients with chronic co-morbidities who were unable to reach their BP goal. Even though amlodipine is documented to cause pedal edema, the side effect was attenuated by the inclusion of hydrochlorothiazide. Similarly the side effects of hydrochlorothiazide (namely hypokalemia) were ameliorated by the addition olmesartan, which is known to cause hyperkalemia. Hence this particular triple drug combination is proven as best. The combination of olmesartan and hydrochlorothiazide has shown good efficacy and a favorable safety profile in a number of clinical trials. The rationale of this combination is related not only to an increased BP- lowering effect, but also to the favorable impact on several pharmacological mechanisms of hypertension. HCTZ is a thiazide diuretic commonly used in combination with other antihypertensive agents such as ARBs. The reflex activation of the RAAS by HCTZ provide strong rationale for the combination of this molecule with an ARB such as olmesartan. Studies show that treatment with olmesartan/ HCTZ is effective in achieving and maintaining 24- hour BP control in various types of hypertensive patients, including those with T2DM and the elderly.

Bisoprolol and amlodipine fixed dose combination have showed to improve response rate, with a similar safety profile when compared with amlodipine and bisoprolol in monotherapy. This combination has shown excellent response in low doses and the antihypertensive effect was greater than the individual monotherapy. Beta blockers suppress renin secretion which potentiates the vasodilatory properties of calcium channel blockers, this results in complementary pharmacological actions and hence additive BP reduction. The combination produces hypotension

and bradycardia and thus cardiac function has to be monitored especially in patients predisposed to heart failure. The acute adverse hemodynamic effect of beta-blocker may be reduced when amlodipine is added.

There have been no established studies indicating safety and efficacy on FDC like nebivolol/ s-amlodipine. The current study identified that the FDC of nebivolol/ s- amlodipine lacks established evidence of safety over single compounds administered separately. This combination produces hypotension and bradycardia, and hence cardiac function must be monitored.

The FDC of amlodipine and atenolol does not possess established evidence of efficacy and safety over single compounds administered separately. One of the reasons for combining a calcium channel antagonist with a ARB in the treatment of mild- moderate hypertension is that latter should improve the patient tolerability of the former by preventing any initial reflex tachycardia. The combination produces hypotension and bradycardia, and hence cardiac function must be monitored especially in patients with predisposing factor. Studies showed that the safety profiles of this combination are comparatively poor when compared to other calcium channel antagonist and ARB combinations.

The combination therapy with cilnidipine and telmisartan can be used safe and effectively in hypertensive patients. Findings suggest that patients with poorly controlled hypertension despite ARB monotherapy may respond well to the combination therapy. This combination is preferred because of fully additive BP reduction. Cilnidipine can be used in combination with an ARB to control blood pressure without any significant adverse effects, and also that cilnidipine successfully reduces elevated heart rate, which is a possible risk factor for cardiovascular events.

The FDC of telmisartan and hydrochlorothiazide has advantage of improved efficacy since RAAS inhibitor and diuretic combination will offset the diuretic induced increase in plasma renin activity and the salt loss will add to the antihypertensive effect of RAAS blockers. Beside, an ARB will also attenuate the metabolic effects of thiazide diuretics like hypokalemia and hyperglycemia. This combination of a RAAS blocker and a low dose thiazide is useful if treatment with a CCB cannot control BP in patients with hypertension.

The FDC of telmisartan and amlodipine was found to be safe and efficacious option for the long-term treatment of hypertension. The use of ARBs and CCB combination may be more appropriately used for those with diabetes and/or metabolic syndrome as these medications do not worsen the metabolic complications. The complementary mechanisms appear to enhance the effectiveness by potential synergistic effects on endothelial function, while reducing some of the negative effects produced by amlodipine, such as peripheral edema.

There have been no established studies indicating safety and efficacy on the fixed dose combination of metoprolol/ olmesartan. The beta blocker and ARB combination provides a little reduction in lowering BP. However these agents are commonly combined and are recommended for systolic heart failure or post-MI patients.

The FDC of losartan and amlodipine has a proven efficacy and safety profile in the management of hypertension especially those blood pressure targets are not achieved with monotherapy. The pharmacological rationale of the combination therapy is achieved through the removal of angiotensin II effect and enhancement of kinin-mediated vasodilation by ARB and decreased vascular resistance by vascular smooth muscle relaxation with CCBs. The combination is proven to reduce edema formation as a result of reduced hydraulic pressure in capillaries. Studies have proven that low dose of amlodipine and losartan at higher dose has a very good tolerability profile with low incidence o adverse events.

The FDC of ramipril and amlodipine has an advantage of improved reduction in ambulatory and office measured BP compared with amlodipine monotherapy. Apart from the comparable BP reduction, numerous studies indicate a reduction in CV death and MI compared with an ACEI/diuretic combination. The side effects between the two pharmacological groups are counteracted. ACEI counteract the dihydropyridine CCB induced activation of sympathetic nervous system (tachycardia), and also partially neutralizes the dose dependent peripheral edema caused by CCBs.

The fixed dose combination of Ramipril and Metoprolol is found to be safe in mild to severe hypertension, since combination of a b-blocker with an ACE inhibitor lowered diastolic BP significantly more than monotherapy. While the lowering of cardiac output and elevation of vascular resistance produced by the b-blockers was attenuated by addition of the ACE inhibitor. Moreover, the combination also caused neutralization

of the undesirable vasoconstrictive amplification. Another important concern is the costlier availability of the combination in comparison to individuals.

The scores obtained in the present study range between 6-13 . Nebivolol/S-amlodipine scored 6, Amlodipine/Atenolol scored 8, six FDCs scored 11, Telmisartan/Cilnidipine scored 12 and four FDCs scored 13. The scoring obtained by each FDCs in the present study is shown in table 4. Figure 6 shows the score distribution of the antihypertensive FDCs prescribed in the present study.

Four FDCs prescribed in the study (Ramipril/Amlodipine, Olmesartan/Metoprolol, Losartan/Amlodipine and Telmisartan/Cilnidipine) reported no side effects. Side effects were managed by replacing one FDC with another or by initiating a monotherapy. In this study,

Ramipril/Metoprolol was not included in the figure showing the distribution of the sample according to fixed dose combination currently prescribed as it was replaced by Olmesartan/Amlodipine to manage the side effect. Only in one prescription, an FDC (Olmesartan/Amlodipine) was changed to monotherapy.

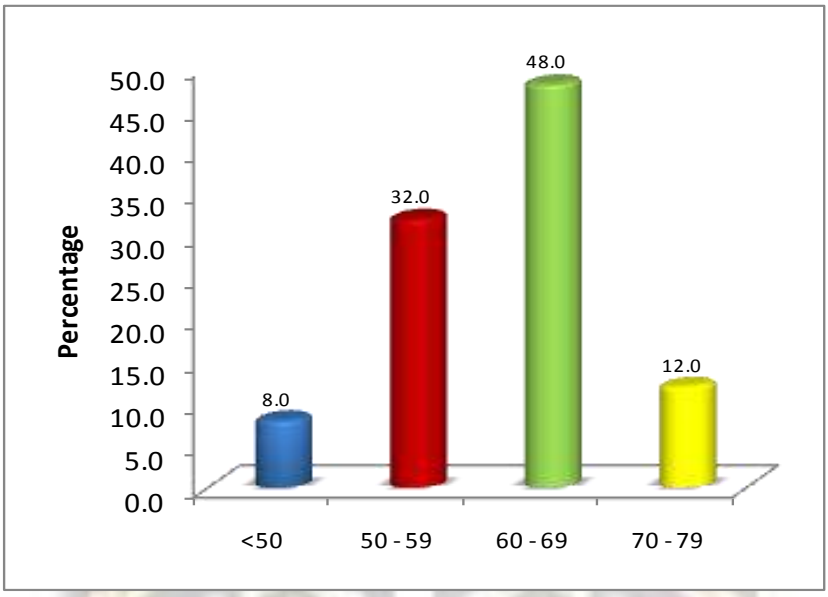

Figure.1 Distribution of the sample according to age

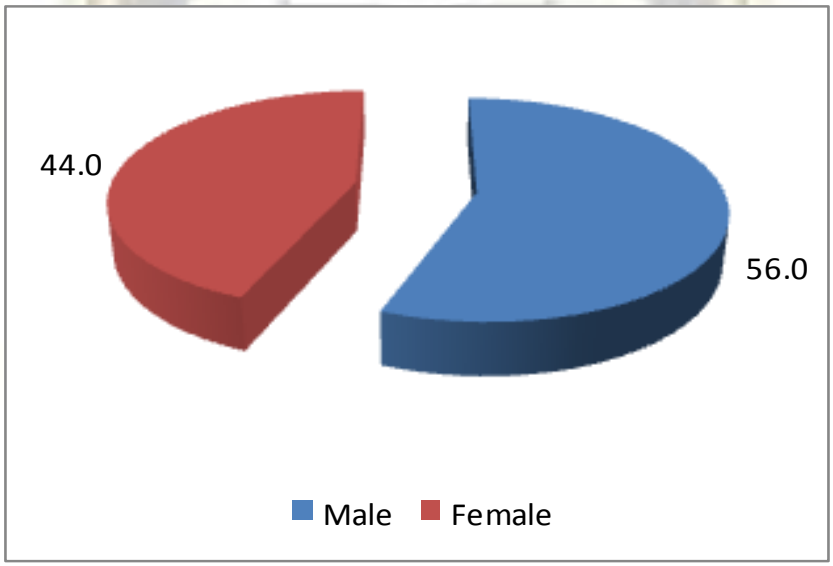

Figure 2: Distribution of the sample according to sex

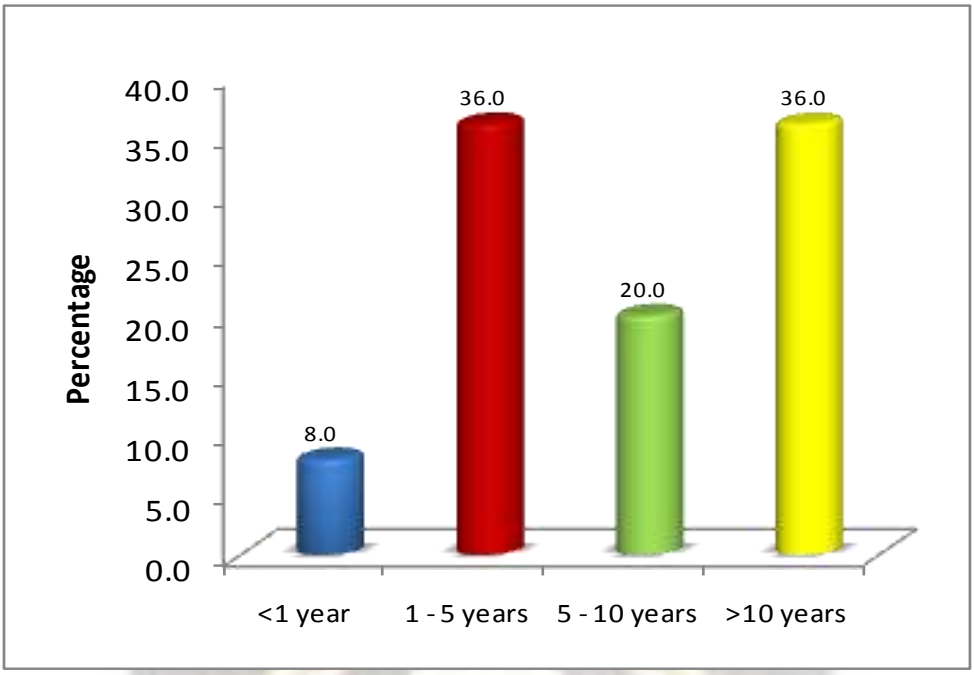

Figure 3 Distribution of the sample according to duration of hypertension

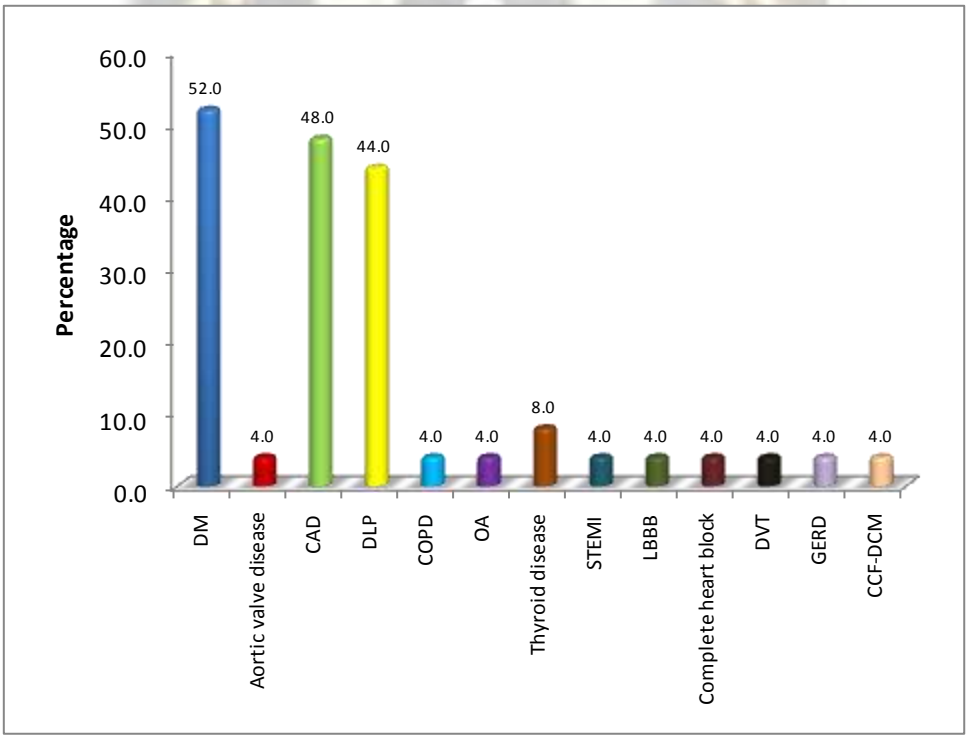

Figure 4: Distribution of the sample according to co morbidities

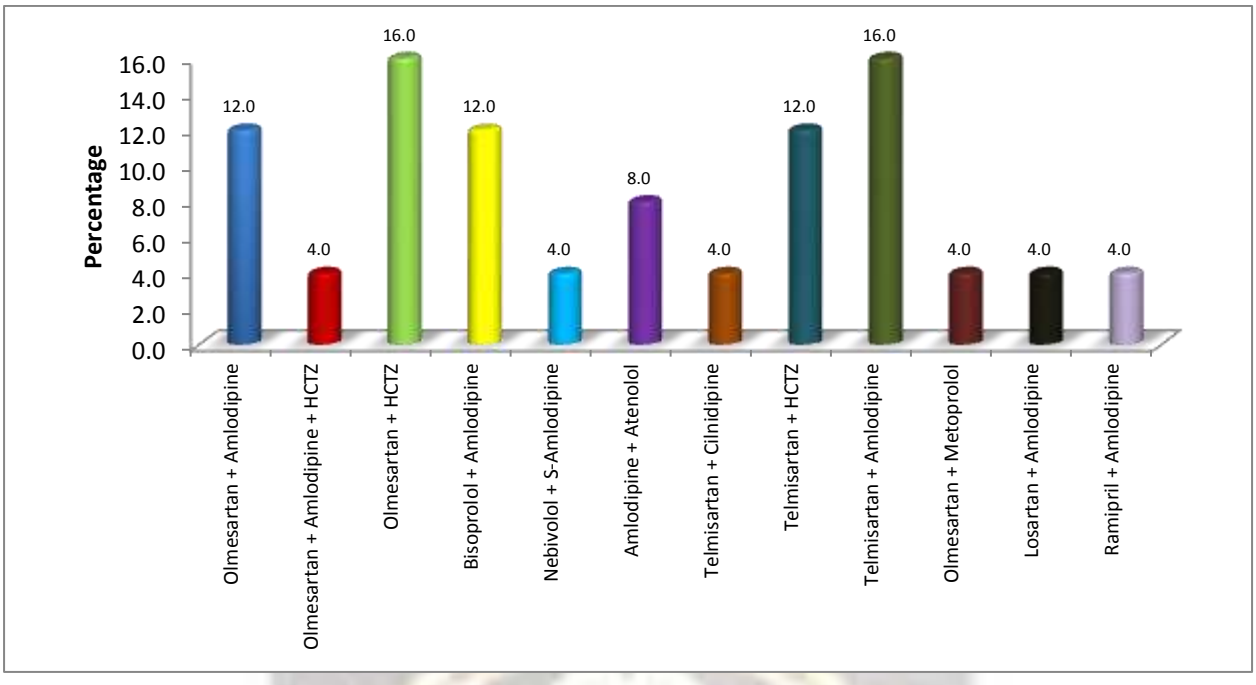

Figure 5 Distribution of the sample according to fixed dose combination prescribed

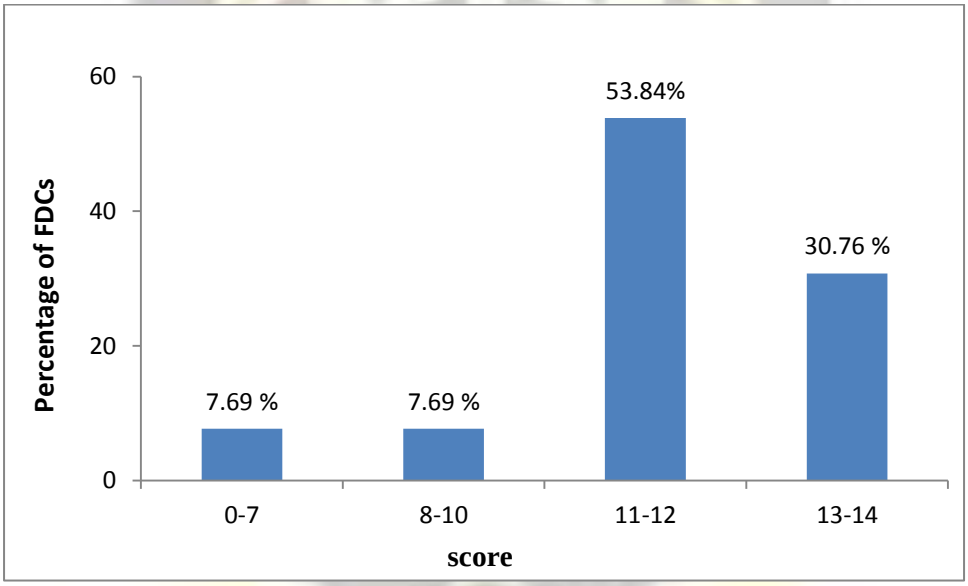

Figure 6: Score distribution of antihypertensive FDCs

CONCLUSION

As our Indian market is flooded with a large number of drugs, both single and fixed dose combinations, there is an immense need to assess whether these drugs are rational and efficacious or not . FDC's in particular are important since most of the FDC's are facing a ban. During this limited study period with only 13 anti-hypertensive FDCs, we were able to find an irrational FDC, which clearly show an urgent need to conduct further studies on evaluating the rationality of FDCs

as a whole. As a clinical pharmacist, our immense role in evaluating the rationality of FDCs could enable the DCGI to withdraw irrational FDCs from the market.

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