African Journal of Pharmaceutical Research and Development
Available online at https://ajopred.com
Vol. 16 No.1; pp. 81-90 (2024)

Original Research Article

DISTRESS ASSOCIATED WITH SIDE EFFECTS OF CALCIUM CHANNEL BLOCKERS AMONG A COHORT OF NEWLY DIAGNOSED WITH HYPERTENSION

PAUL OTOR ONAH[1,*], ABDULATEEF SIYAKA[1], KENNEDY EMEKA OLUIGBO[2]

1. Department of Clinical Pharmacy and Pharmacy Administration, University of Maiduguri, Borno State, Nigeria
2. Department of Clinical Pharmacy and Biopharmaceutics, Enugu State University of Science and Technology, Enugu State, Nigeria

ABSTRACT

Antihypertensive therapy with calcium channel blockers (CCBs) is reported to be frequently associated with varying levels of distress due to their side effects. The severity of distress may result in patients intentionally interrupting or withdrawing from therapy. In clinical settings, distress from side effects of drug(s) are sometimes left unreported, overlooked or poorly resolved by clinicians. The aim of this study was to assess distress due to side effects of commonly prescribed CCB-based antihypertensive therapies.This was a prospective observational study among patients newly diagnosed with primary hypertension being treated with either CCB monotherapies or combination regimens as initial therapy. A total of 180 patients enrolled completed the eight week study and their data used in final analysis. The subjects were allocated into six treatment groups of 30 each and given either amlodipine 10mg, nifedipine 20mg, bendrofluthiazide (monotherapies) or their combinations with bendrofluthiazide 5mg or Lisinopril 5mg (dual therapies). The level of distress before and after initiation of therapy was compared using Students t test and P values ≤ 0.05 was considered statistically significant. Patients on dual therapies reported more side effects compared to monotherapies. The most commonly reported side effects included loss of libido (38% - 47%), pitting edema (28% - 35%), headache (26% - 36%), muscle cramps (9% - 18%) and fatigue (17% - 30%). Distress score of monotherapies (14.9) and dual therapies (15.3) was considered mild (< 25 threshold). There was significant reduction in distress with bowel upset (P = 0.001), insomnia (P = < 0.001), pain (P = 0.001), breathing difficulties (P = 0.009) and concentration for BDF containing regimen (P = 0.001). Distress among Lisinopril containing regimens involved appetite (P = 0.003), pain (P = 0.002) and fatigue (P = 0.003). Overall, distress due to side effects was mild for all the antihypertensive drug(s).

ARTICLE INFO

Received 08 November, 2023
Accepted 13 March, 2024
Published 29 April, 2024

KEYWORDS

Antihypertensives,
Calcium channel blockers,
Distress,
Hypertension,
Nifedipine,
Side effects

INTRODUCTION

Hypertension is estimated to affect a quarter of adult population and among the leading causes of premature mortality globally [1]. It is a disorder of multifactorial etiology involving complex interplay of both modifiable and non-modifiable risk factors that predispose individuals to the disease. Some of the modifiable factors include risky lifestyle, environmental and socioeconomic determinants [2, 3] as well as other contributors such as mental health disorders [4, 5], work related stress [6, 7], sleep disorders

***Corresponding author:** onahpaul@unimaid.edu.ng; +234-803 8258 589

https://doi.org/10.59493/ajopred/2024.1.9 ISSN: 0794-800X (print); 1596-2431 (online)

[8], anxiety disorders [9] and depression [10]. While the relationship between psychosocial factors and hypertension remain unclear [11 – 13], patients have been frequently reported to have depressive symptoms, although this conclusion remain disputed [14].

The incidence of psychological distress among hypertensive patients [15, 16] is believed to arise partly from increased burden of using healthcare services [17]. Although the relationship between anxiety disorders and higher risk of hypertension has been reported [17, 19], arguments of which one precede the other still persist [16, 20]. A recent study reported that anxiety may even contribute to lowering blood pressure among hypertensive patients [21].

The most widely used definition of "symptoms distress" referred it as "the degree of discomfort experienced from specific symptoms as reported by patients" [22]. Medication therapy is frequently associated with side effects of varying level of severity in the course of short or long term drug therapy management. Some of these side effects have often been mistaken for either symptoms of existing diseases, worsening of symptoms or even an onset of a new disease(s). When side effects are severe enough patients may intentionally discontinue or sub optimally adhere to therapy with consequent loss of clinical benefits [23].

Hypertension is largely asymptomatic in the early stages of the disease and the late stage symptoms due to secondary complications are not specific enough to be used for clinical diagnosis. The side effect profile of antihypertensive drug(s) vary widely depending on the class of drug(s), duration of therapy, polypharmacy as well as dosage of drugs, all of which have profound effect on patients quality of life [24].

In recent years, calcium channel blockers [CCBs] are increasingly prescribed as drugs of first choice in the management of essential hypertension. This is partly driven by their low cost, wide margin of safety and clinical effectiveness in achieving sustained blood pressure reduction [25]. The most widely used CCBs include amlodipine and nifedipine both of which are equally effective in the management of essential hypertension. These drugs are associated with the development of varying degrees of peripheral edema [26] which is a known class effect found among other dihydropyridine CCBs. Distress caused by CCB induced peripheral edema has been reported although its impact on blood pressure control and patients quality of life is less reported in the country [27, 28].

The widespread prescription of CCB based monotherapy with amlodipine and nifedipine as well as their combinations with diuretics and angiotensin converting enzyme inhibitor has not received adequate assessment of distress caused by side effects by these therapies. This study therefore aim to identify common side effects of six CCB based antihypertensive therapies and associated distress among patients newly diagnosed with hypertension.

METHODS

Study Setting

This study was carried out in General Hospital North Bank Makurdi and Bethesda Hospital Oju in Benue State Nigeria.

Study Design

This was a prospective open label observational study involving newly diagnosed hypertensive patients treated with amlodipine 10 mg or nifedipine 20 mg monotherapies and their combinations with bendrofluthiazide 5 mg or lisinopril 5 mg.

Eligibility Criteria

1. Newly diagnosed patients with hypertension (≥ 140/90 mm/Hg)
2. Patients with no pre-existing chronic disease
3. Age ≥ 30 years
4. Women must not be pregnant

Sample Size

The two health facilities recorded an average of 320 new cases of primary hypertension weekly and about 1300 monthly over the previous six months. The weekly average of new cases was used to calculate sample size because of challenges with finding eligible subjects. The sample size was calculated using Taro Yamane's formula which gave 177 at 95% confidence interval and 5% precision level. The study involved enrolment of 198 subjects who met inclusion criteria; however 180 completed the study giving an attrition rate of 9%.

Subject Enrolment

Patients who met eligibility criteria were recruited from the hospitals outpatient departments following diagnosis of essential hypertension. All enrollees provided informed consent after receiving adequate explanation of the study protocol and their right of exit at any point in time. They were divided into six groups based on physician's clinical decision and blood pressure level at the point of enrollment. Patients with initial systolic blood pressure of ≥ 160 mm/Hg and/or diastolic blood pressure of ≥ 100 mm/Hg were allocated to combination therapy groups, while those below this blood pressure target were allocated into monotherapy groups. Those allocated to monotherapies received either daily Amlodipine 10mg ($n = 30$) or Nifedipine 20mg ($n = 30$) daily while combination therapy group received either Amlodipine 10mg + Bendrofluthiazide 5mg ($n = 30$), Nifedipine 20mg + Bendrofluthiazide 5mg ($n = 30$), Amlodipine 10mg + Lisinopril 5mg ($n = 30$), Nifedipine 20mg +Lisinopril 5mg ($n = 30$). The blood pressure and side effects reported by patients were recorded at biweekly intervals until the end of study.

Measurement of Blood Pressure

The measurement was carried out by a qualified nurse with mercury sphygmomanometer after ten minutes rest. The cuff was placed on the upper left arm, secured and rested on table at level with the left arm. The stethoscope was placed over the brachial artery and the cuff pumped slowly while listening to the

pulse. When the pulse sound disappeared, the cuff was slowly deflated while reading the mercury level in the sphygmomanometer. The reading when pulse sound reappeared was recorded as systolic blood pressure [SBP] and at the point pulse sound disappeared was recorded as diastolic blood pressure [DBP]. The process was repeated for each blood pressure [BP] measurements five minutes apart and average taken as the patient's blood pressure.

Symptoms Distress Scale Questionnaire/Administration

The "symptoms distress scale" which is a ten item instrument was self-administered on the first day of therapy and at fourth and eighth week of the study. The instrument had item scores of 1 – 5 (*1 – no distress, 2 – mild distress, 3 – moderate distress, 4 – high distress, 5 – severe distress*). A mean summary score of < 25 is considered mild, 25 – 33 is moderate and 33 and above is considered severe distress [22, 29]. They also report side effects experienced in the course of the study and those who were not literate were assisted by trained nurses who also assisted with BP measurements.

Data Collection

Enrollees were divided to six treatment groups based on drug(s) prescribed. The attending physician decided the drug(s) to be prescribed based on clinical assessment and the groups were identified by the use of codes. Demographic data and other relevant medical information was extracted from patient records. The initial BP was measured on the first date of enrolment and subsequently repeated after each clinical consultation until the end of the study period. The drug(s) were all provided free of charge for the duration of the study.

Data Analysis

The data was entered into Microsoft excel and cleaned before being loaded in to SPSS version 21 for descriptive and inferential statistics. The mean score of each distress domain was calculated for each of the six treatment groups (pre-treatment and post-treatments) according to standard procedure [22, 29]. The mean distress scores between pre and post treatment was compared using Students t test to indicate if significant differences occurred during the study period. P values of ≤ 0.05 was considered statistically significant.

Ethical Approval

This was obtained from health research ethics committee Benue State Ministry of Health (MOH/STA/204/vol.1/118).

RESULTS

The demographic data showed that males accounted for about two thirds of subjects (n = 112, 62.3%). Majority of subjects had no formal education (n = 69, 38.3%) and only about a quarter had tertiary level education (n = 38, 21.7%). The major occupation of respondents were business (n = 82, 45.1%), farming (n = 53, 29.5%) and civil service (n = 45, 25.4%). The mean age was 54.5 ± 10.9 years (Table 1).

There was significant reduction of both SBP (P = 0.0001) and DBP (P = 0.009) in all treatment groups. The reductions were significant with monotherapies (P = 0.043), bendrofluthiazide (BDF) containing regimens (P = 0.0001) and Lisinopril containing regimens (P= <0.001). While SBP reduction between amlodipine and nifedipine therapies was significant (P = 0.043), there reduction was insignificant with DBP (P = 0.772). Dual therapies however produced significant reductions with BDF (P = 0.001) and lisinopril (P = 0.016) combination regimens (Table 2).

Patient reported side effects with monotherapies slightly varied between amlodipine and nifedipine treated groups. The most common side effects included reduction/loss in libido particularly among males (n = 112, 38.7% – 41.2%), followed by pitting edema (n = 60, 28.5% – 29.2%) and headache (n = 60, 26.9% – 29.7%). Other frequently reported side effects included fatigue (n = 60, 17.4% – 18.6%) and muscle cramping (9.5% – 11.4%) (Figure 1).

The prevalence of side effects was slightly higher with BDF treated groups compared to those on lisinopril as add on drug. The prevalence of pitting edema in BDF treated groups was between 33.3% - 35% (n = 60) compared to lisinopril treated groups (n = 60, 14.2% – 17.5%). Headaches was reported by 29.2% - 36.7% patients (n = 60) among BDF treatment groups compared to 23.3% - 24.2% with lisinopril groups (n = 60). The same pattern of report was observed with loss of libido in BDF groups (45.0% - 47.5%) compared to 14.2% - 17.5% with lisinopril groups. Muscle cramp was more frequently reported among BDF treated groups (16.7% - 18.3%) compared to 6.7% - 7.5% observed among lisinopril treated patients (Figure 2).

Distress from the side effects of monotherapies was mild (< 25 threshold), although significant decline was found with insomnia (P = 0.002), pain (P = 0.003) and bowel upset (P = 0.007) (Table 3).

Distress associated with BDF add on therapy was mild (< 25 threshold), however the addition of BDF to amlodipine or nifedipine significantly reduced distress related to insomnia (P = 0.043), pain (P = 0.001) and bowel upset (P = <0.001) (Table 4).

The addition of Lisinopril to amlodipine or nifedipine therapy significantly increase distress from appetite (P = 0.003) and pain (P = <0.001), although there was reduction in distress from fatigue (P = 0.002). The level of distress from lisinopril addition was mild with no significant change from baseline values (Table 5).

DISCUSSION

Antihypertensive therapy with CCB based monotherapies or combinations with BDF or lisinopril did not produce any significant rise in distress from side effects. While patients on dual therapies with BDF reported slightly higher prevalence of side effects, the associated distress was generally mild comparable to previous studies [30]. The antihypertensive drug regimens used in this study produced significant reduction in SBP, although the fall in DBP was only significant with dual

Table 1: Demographic data (n = 180)

Variable	Number (%)
Gender	
Male	112 62.2)
Female	68 (37.8)
Marital status	
Single	22 (11.4)
Married	125 (64.7)
Divorced	26 (13.5)
Widowed	20 (10.4)
Education	
No formal education	69 (38.3)
Primary	26 (14.4)
Secondary	46 (25.6)
Tertiary	39 (21.7)
Occupation	
Farming	53 (29.5)
Civil service	45 (25.0)
Business	82 (45.5)
Age (years)	
30 – 40	19 (10.6)
41 - -50	44 (24.5)
51 – 60	62 (34.4)
61 – 70	42 (23.3)
≥ 71	13 (7.2)
Mean	54.5 ± 10.9

Table 2: Comparison of efficacy of antihypertensive drug(s)

Regimen	Pre-treatment Mean (SD)	Post-treatment Mean (SD)	t - value	P value
SBP (mm/Hg)				
AML	178.2 (11.2)	139.3 (6.8)	15.71	<0.001
NIF	168.5 (8.2)	135.2 (7.4)	14.77	<0.001
AML vs NIF	*t=3.44 (P=0.001)*	*t=2.08 (P=0.043)*		
AML+BDF	165.9 (7.4)	137.9 (5.8)	19.30	<0.001
NIF+BDF	159.8 (6.2	132.7 (4.1)	23.63	<0.001
AML+BDF vs NIF+BDF	*t=0.29 (P=0.770)*	*t=1.76 (P=0.083)*		
DBP (mm/Hg)				
AML	103 (8.2)	86. (4.2)	9.71	<0.001
NIF	106.5 (6.9)	85.7 (3.8)	12.62	<0.001
AML vs NIF	*t=1.41 (P=0.163)*	*t=0.36 (P=0.722)*		
AML+BDF	110.2 (6.2)	88.3 (3.5)	21.75	<0.001
NIF+BDF	104 (5.1)	90.1 (2.7)	21.48	<0.001
AML+BDF vs NIF+BDF	*t=6.62 (P=<0.001)*	*t= 2.64 (P=0.001)*		
AML+LIS	109.1 (4.3)	89.2 (5.7)	14.98	<0.001
NIF+LIS	105 (3.2)	92.3 (1.6)	21.48	<0.001
AML+LIS vs NIF+LIS	*t=3.85 (P=<0.001)*	*t=4.48 (P=0.016)*		

Key*: AML – Amlodipine, NIF – Nifedipine, BDF – Bendrofluthiazide, LIS - Lisinopril*

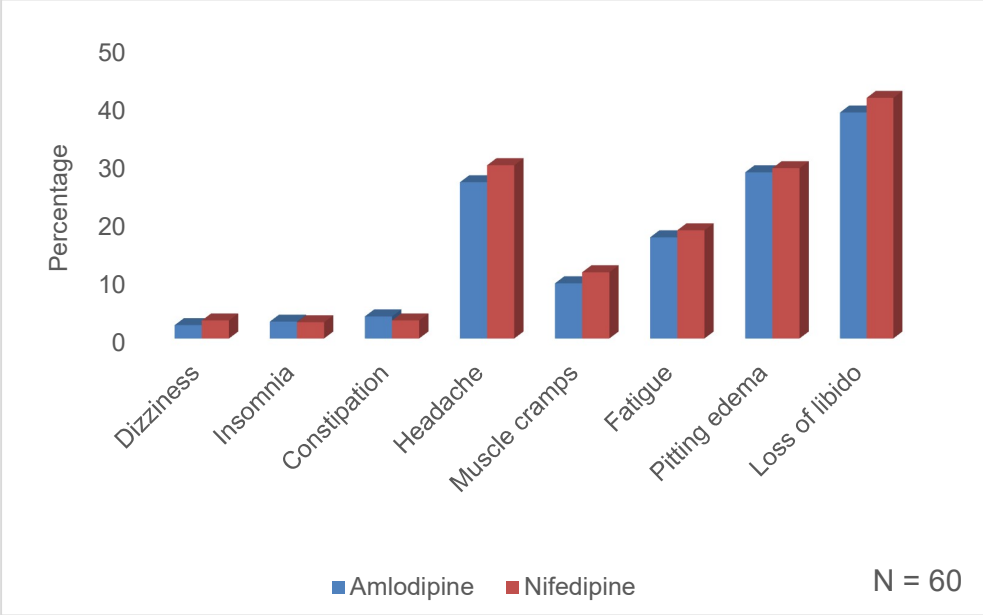

Figure 1: Prevalence of side effects with monotherapies

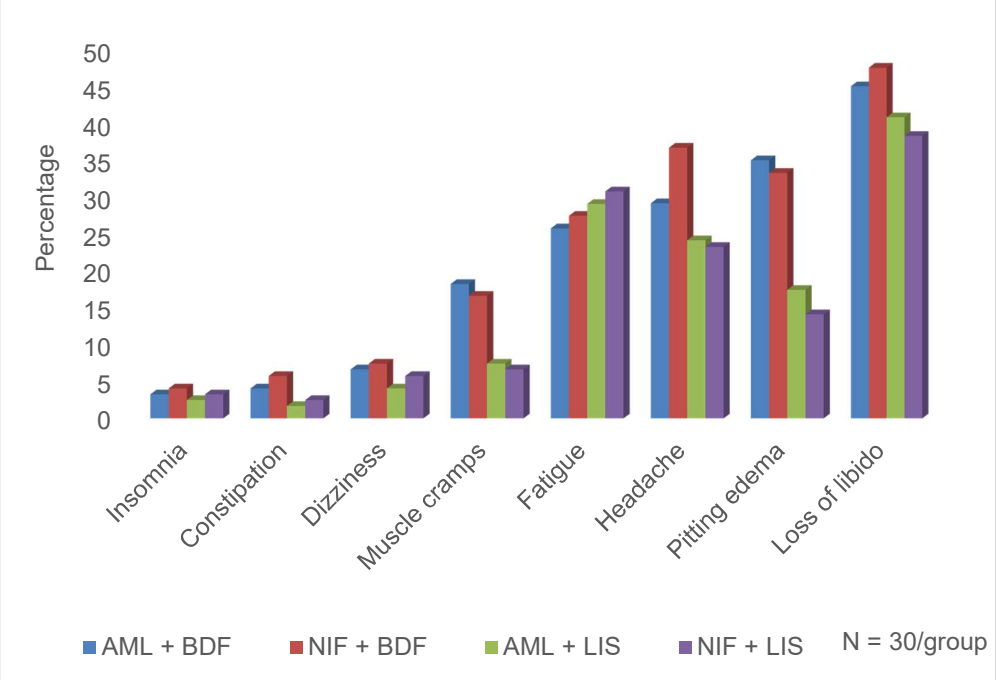

Figure 2: Prevalence of of side effects with dual therapies

Table 3: Distress associated with Amlodipine and Nifedipine monotherapies

Variable	**Amlodipine** (*n=30*)			**Nifedipine** (*n=30*)		
	Pretest Mean (SD)	**Posttest Mean (SD)**	**P value**	**Pretest Mean (SD)**	**Posttest Mean (SD)**	**P value**
Nausea	1.25 (0.67)	1.24 (0.49)	0.867	1.25 (0.67)	1.22 (0.40)	0.616
Appetite	1.38 (0.49)	1.47 (0.56)	0.094	1.41 (0.49)	1.50 (0.57)	0.097
Insomnia	1.85 (0.82)	1.71 (0.72)	0.075	1.88 (0.53)	1.69 (0.47)	<0.001↓
Pain	1.88 (0.54)	1.74 (0.51)	0.009↓	1.88 (0.53)	1.69 (0.47)	<0.001↓
Fatigue	1.47 (0.51)	1.50 (0.56)	0.582	1.47 (0.51)	1.53 (0.57)	0.276
Bowel upset	1.38 (0.49)	1.26 (0.45)	0.010↓	1.41 (0.49)	1.28 (0.46)	0.007↓
Concentration	1.24 (0.43)	1.24 (0.43)	1.000	1.25 (0.44)	1.25 (0.44)	1.000
Breathing	1.21 (0.43)	1.12 (0.41)	0.036↓	1.13 (0.34)	1.13 (0.42)	1.000
Cough	1.24 (0.43)	1.18 (0.39)	0.152	1.19 (0.39)	1.16 (0.37)	0.439
Outlook	2.12 (1.41)	1.91 (1.11)	0.105	2.03 (1.40)	1.88 (1.13)	0.247
Sum	**15.03 (6.27)**	**14.37 (5.63)**	**0.277**	**14.90 (6.11)**	**14.33(5.61)**	**0.340**

Key: ↑ - *increase,* ↓ - *decrease*

Table 4: Distress associated with CCB/BDF therapy

Variable	**AML+BDF** (*n=30*)			**NIF+BDF** (*n=30*)		
	Pretest Mean (SD)	**Posttest Mean (SD)**	**P value**	**Pretest Mean (SD)**	**Posttest Mean (SD)**	**P value**
Nausea	1.08 (0.27)	1.11 (0.39)	0.380	1.10 (0.29)	1.14 (0.42)	0.277
Appetite	1.29 (0.46)	1.29 (0.51)	1.000	1.31 (0.47)	1.31 (0.52)	1.000
Insomnia	2.03 (0.91)	1.84 (0.72)	0.023	2.00 (0.91)	1.83 (0.73)	0.044
Pain	1.89 (0.56)	1.68 (0.47)	**0.001**↓	1.88 (0.55)	1.71 (0.51)	**0.018**↓
Fatigue	1.39 (0.49)	1.39 (0.55)	1.000	1.43 (0.50)	1.10 (0.29)	0.571
Bowel upset	1.29 (0.46)	1.08 (0.270	**0.001**↓	1.29 (0.46)	1.10 (0.29)	**0.001**↓
Concentration	1.18 (0.39)	1.05 (0.23)	**0.001**↓	1.17 (0.38)	1.17 (0.38)	1.000
Breathing	1.08 (0.27)	1.05 (0.23)	0.241	1.14 (0.42)	1.05 (0.22)	**0.009**↓
Cough	1.21 (0.41)	1.18 (0.39)	0.462	1.26 (0.44)	1.21 (0.41)	0.249
Outlook	2.16 (1.52)	1.92 (1.24)	0.090	2.26 (1.55)	2.00 (1.29)	0.074
Sum	**14.39(5.65)**	**13.42(5.18)**	**0.079**	**16.1 (5.79)**	**13.90 (5.09)**	**0.001**↓

Key: ↑ - *increase,* ↓ - *decrease*

Table 5: Distress associated with CCB/LIS therapy

Variable	AML+LIS [*n=30*]			NIF+LIS [*n=30*]		
	Pretest Mean (SD)	Posttest Mean (SD)	P value	Pretest Mean (SD)	Posttest Mean (SD)	P value
Nausea	1.50 (0.79)	1.62 (0.79)	0.136	1.50 (0.79)	1.62 (0.79)	0.136
Appetite	1.35 (0.65)	1.55 (0.65)	0.003↑	1.35 (0.65)	1.55 (0.65)	0.003↑
Insomnia	1.76 (0.74)	1.86 (0.74)	0.185	1.76 (0.74)	1.86 (0.74)	0.185
Pain	1.71 (0.52)	1.91 (0.52)	0.002↑	1.72 (0.53)	1.72 (0.53)	1.000
Fatigue	1.62 (0.74)	1.44 (0.61)	0.002↓	1.69 (0.76)	1.48 (0.63)	0.003↓
Bowel upset	1.47 (0.71)	1.35 (0.69)	0.093	1.55 (0.74)	1.41 (0.73)	0.062
Concentration	1.18 (0.46)	1.24 (0.61)	0.276	1.17 (0.47)	1.24 (0.64)	0.221
Breathing	1.38 (0.85)	1.29 (0.79)	0.282	1.41 (0.91)	1.34 (0.86)	0.438
Cough	1.53 (0.66)	1.50 (0.66)	0.655	1.55 (0.69)	1.52 (0.69)	0.669
Outlook	2.15 (1.33)	1.91 (1.21)	0.064	2.07 (1.25)	1.86 (1.12)	0.099
Sum	**15.7 (7.5)**	**15.1 (7.3)**	**0.447**	**15.2 ([7.3)**	**15.3 (7.5)**	**0.432**

Key: ↑ - *increase*, ↓ - *decrease*

therapies similar to previous studies [31 – 33]. The mixed results from BP reduction achieved with monotherapies as well as dual therapies may be related to multiple variables such as initial BP, age and other patient specific variables.

The most frequently reported side effect was comparatively similar to previous studies with some of them predictable from known pharmacological actions of the drugs [34, 35]. Among these is the incidence of peripheral edema which is associated with all CCBs, although prevalence vary widely in severity between individual drugs and patients [36, 37]. The side effects of CCBs is independent of their efficacy in lowering elevated BP [38 - 40] and other cardiovascular benefits [41, 42]. While the addition of BDF appeared to increase side effects such as pedal edema, headaches, reduced libido, fatigue, muscle cramps and constipation, they are largely predictable [43, 44].

The prevalence of these side effects vary widely among patients and may be related to age, intolerance, patient health status among other factors [45, 46]. These side effects have been reported to be responsible for suboptimal adherence [35], increased risk of depression [47], metabolic abnormalities [48, 49], insomnia [50 – 52] and cough [53]. Distress from CCB based therapies was generally mild with no significant rise from pretreatment values. The significant reduction of distress recorded with respect to insomnia, bowel upset, fatigue and pain may be related to improved psychological response to therapy, rather than the pharmacological actions of the drug(s) [54]. The effect of CCBs in pain modulation have received research interest in recent years, however their efficacy in pain reduction has yet to be clinically proven [55].

The impact of side effects on distress have been reported to be influenced by a number of factors including older age, comorbidity, high drug dosage and polypharmacy [56 – 58]. While individual response to side effect mediated distress may be influenced by sociodemographic and psychological factors [59], pharmacotherapy with CCBs offer patients superior long term clinical benefits even in the presence of mild distress [46]. It is therefore important for pharmacists to take into cognizance possible distress from medication side effects in the course of providing pharmaceutical care services. Distress can also be used as an early indicator of poor humanistic outcome and a good predictor of long term non-adherence in hypertension management.

CONCLUSION

The distress caused by CCB based antihypertensive therapy was mild with no significant difference from pretreatment levels. While dual therapies witnessed higher incidence of side effects, there appeared to be little difference in distress from amlodipine and nifedipine monotherapy and their combination with BDF and lisinopril. Distress assessment following drug therapy need to be considered for long term antihypertensive therapy.

ACKNOWLEDGEMENTS

The support of physicians, nurses and pharmacists in patient enrolment, questionnaire administration and follow up assessment is hereby acknowledged.

FUNDING

This study was supported with funds obtained from Tertiary Education Trust Fund (TERTFUND) institution based research grant of the University of Maiduguri, Borno State Nigeria.

CONFLICT OF INTEREST

The authors declare no conflict of interest,

AUTHOR'S CONTRIBUTIONS

Onah PO: Concept, study design, data collection analysis, literature review, manuscript review. Siyaka A: Study design, data collection, analysis, literature review, manuscript review
Oluigbo KE: Data analysis, literature review, manuscript draft

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