A Profile of Adverse Effects of Antihypertensive Medicines in a Tertiary Care Clinic in Nigeria

Abimbola O. Olowofela, Ambrose O. Isah
Department of Medicine, Clinical Pharmacology and Therapeutics Unit, University of Benin, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria

Abstract

Background: There has been a dearth of comprehensive data on the profile of adverse reactions to antihypertensive medicines in the Nigerian setting despite increased use. Objective: This study was aimed to characterize the adverse reactions experienced in the homogenously black African population. Methods: The study was carried out at the University of Benin Teaching Hospital, Benin City, Nigeria, in consenting eligible hypertensive patients ≥18 years. Adverse reactions were sought using patient’s self-report and a medicine-induced symptom checklist. Results: A total of 514 patients (340 females) aged 22–97 years were studied. Thirteen percent, 27.6%, 26.7%, 22.0%, and 10.7% were on 1, 2, 3, 4, and ≥5 medicines, respectively, for control of their blood pressure with the frequency of adverse effects increasing proportionately up to four medicines. Adverse reactions to antihypertensive medicines were reported by a total of 93 (18.1%) patients. Diuretics – 27.9%, calcium channel blockers (CCBs) – 26.8%, and angiotensin-converting enzyme inhibitors (ACEIs) – 26.8% accounted for most of the adverse reactions seen, notably frequent micturition and headaches (CCB); excessive micturition and dizziness (diuretics); dry irritating cough (ACEI). Notable complaints for all patients using the checklist were increased frequency of micturition, reduction in libido, and headaches. The reactions resulted in the discontinuation and substitution of therapy in 49.5% of the patients. Conclusions: The characterization of these reactions in Nigerians requires further studies as frequent micturition reported is still a neglected complaint in antihypertensive therapy.

Keywords: Adverse drug reactions, antihypertensive agents, Nigeria

Résumé

Contexte: Il y a eu une pénurie de données complètes sur le profil des réactions indésirables aux médicaments antihypertenseurs dans le cadre nigérien malgré une utilisation accrue. Objectif: Cette étude visait à caractériser les effets indésirables de la population africaine homogène noir. Méthodes: L'étude a été réalisée à l'hôpital universitaire de l'Université du Bénin, dans la ville de Benin, au Nigeria, dans des patients hypertendus admissibles ≥18 ans qui ont consenti à l'étude. Des réactions indésirables ont été recherchées en utilisant l'auto-évaluation du patient et une liste de contrôle des symptômes induite par un médicament. Résultats: Un total de 514 patients (340 femmes) âgés de 22 à 97 ans ont été étudiés. Treize pour cent, 27,6%, 26,7%, 22,0% et 10,7% étaient en 1, 2, 3, 4 et ≥5 médicaments, respectivement, pour le contrôle de leur pression artérielle avec la fréquence des effets indésirables augmentant proportionnellement jusqu'à quatre médicaments. Les réactions indésirables aux antihypertenseurs ont été rapportées par un total de 93 patients (18,1%). Les diurétiques - 27,9%, les inhibiteurs des canaux calciques (CCB) - 26,8% et les inhibiteurs de l’enzyme de conversion de l’angiotensine (ACEI) - 26,8% ont représenté la plupart des effets indésirables observés, notamment la miction et les maux de tête fréquents (CCB); Miction excessive et vertiges (diurétiques); Toux irritante sèche (ACEI). Des plaintes notables pour tous les patients utilisant la liste de contrôle étaient une fréquence accrue de miction, une réduction de la libido et des maux de tête. Les réactions ont entraîné l’arrêt et la substitution du traitement chez 49,5% des patients. Conclusions: La caractérisation de ces réactions chez les Nigérians nécessite d’autres études car les mictions fréquentes rapportées sont encore une plainte négligée dans le traitement antihypertenseur.

Mots-clés: Effets indésirables des médicaments, agents antihypertenseurs, Nigéria

Access this article online

Quick Response Code: 
Website: www.annalsafrmed.org
DOI: 10.4103/aam.aam_6_17

Address for correspondence: Dr. Abimbola O. Olowofela, Department of Medicine, Clinical Pharmacology and Therapeutics Unit, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria. E-mail: felabimbola@yahoo.com

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How to cite this article: Olowofela AO, Isah AO. A profile of adverse effects of antihypertensive medicines in a tertiary care clinic in Nigeria. Ann Afr Med 2017;16:114-9.
INTRODUCTION

Hypertension is a global disease considered as the leading risk factor for cardiovascular diseases with significant health burden and accounts for 9.4 million deaths as well as 7.0% disability-adjusted life years (DALYs) of global DALYs in 2010.[1] The prevalence in Nigeria is estimated at over 28.9%.[2] It is associated with a high morbidity and mortality, from increased risks of stroke, ischemic heart disease, renal failure, congestive heart failure as well as hypertensive heart diseases and the observation that it is worse in people of black ancestry.[3-5] The use of medicines and other forms of nonpharmacological therapy in treating hypertension has been shown to reduce this morbidity and mortality.[6,7] There has been a considerable increase in the arsenal of antihypertensive medicines in the past few decades, and their use may be associated with the development of adverse reactions which is likely to result in nonadherence to therapy, increased morbidity and mortality as well as economic consequences.[8,9] It has also led to the withdrawal of some of these medicines from use.[10]

Adverse reactions in out patient care have been estimated to occur in about 25% of patients[11] and factors that have been associated with increased frequency of adverse reactions include, number of medicines taken by the patient’s genetic disposition, age, pregnancy, and exogenous factors such as food and interactions with other medicines.[12] Identification of adverse reactions using different methods has also been advocated to limit the poor prognosis that is associated with adverse reactions.[11] The profile of adverse reactions to antihypertensive medicines in our environment has not been properly characterized given the antihypertensive armamentarium in use in this setting. There is a need to properly characterize the tolerability profile of these medicines in this environment.

METHODS

This cross-sectional study was carried out at the consultant medical outpatient department (COPD) of a tertiary hospital in Southern Nigeria. The teaching hospital is a 730-bed tertiary center, which also serves as a referral center to the neighboring states of Ondo, Anambra, Bayelsa, and Delta states. The COPD houses the hypertension clinic as well as other medical subspecialties. The study was carried out over 9 months and patients with a diagnosis of hypertension on therapy who attended the medical outpatient clinic. Hypertensive patients on antihypertensive medicines who were aged 18 years and above and consented to the study were included in the study.

For this cross-sectional study, the sample size calculation was based on a previous study by Isah et al.[13] on the assessment of patient’s knowledge and experience of hypertension and it revealed that about 24.8% reported that an adverse event affected their compliance. Using this figure as an estimate of the desired proportion of an adverse drug reaction (ADR), at a confidence interval of 95%, the formula for simple proportions was used.[14] A sample of 289 hypertensive patients was the minimum sample size calculated for this study. Furthermore, anticipating a 70% response to the questionnaire a sample size of 376 was estimated. However, 514 patients consented and were recruited into the study.

The patients were classified as being hypertensive (defined according to the Nigerian Hypertension Society guidelines that were based on the 1999 WHO/International Society of Hypertension recommendations), as blood pressure ≥140/90 mmHg.[15] All patients who fulfilled the inclusion criteria and consented to the study were included. During the visit, their demographic characteristics, duration of hypertension as well as comorbidities were recorded in an interviewer-administered questionnaire. Antihypertensive medicines, other prescribed medications and indication for their use were noted, use of other nonprescribed medicines and herbal medicines were also recorded. ADRs to antihypertensive medicines prescribed at the last clinic visit were sought.

Following the self-reported sessions, a modified checklist of antihypertensive medicines – induced symptoms as described by Bulppt and Dollery[16] and modified based on previous studies[13,17] was administered to the patients to determine what symptoms they experienced that was related to medicine use. Reported adverse reactions were also documented and classified using the Medical Dictionary for Regulatory Activities (MedDRA) system organ classification,[18] and the probability of the event being an ADR was assessed with the WHO and Naranjo causality algorithms.[19,20] The outcome of the reaction was noted as well as the action patient took following the ADR.

Ethical considerations

Ethical approval was obtained from the Ethics and Research Committee of the University of Benin Teaching Hospital, and informed consent was obtained from each patient verbally. The quality of the data and its confidentiality were ensured by keeping the patients’ identity coded with their initials only. The data were fully anonymized and aggregated. Any information about any patient was kept strictly confidential and not shared with unauthorized individuals. The patient’s right to confidentiality, information and privacy were respected.

Statistical analysis

Antihypertensive medications were classified into different classes: (angiotensin converting enzyme inhibitors [ACEI], beta-blockers, calcium channel blockers [CCBs], diuretics, centrally acting agents, and angiotensin receptor blockers [ARBs]). Data were analyzed using SPSS (Statistical package for the Social Sciences, SPSS Inc., Chicago, IL, USA) software version 16 for windows. Descriptive and inferential analyses were conducted as appropriate, and level of significance was set at P < 0.005.

RESULTS

A total of 514 patients were recruited into the cross-sectional descriptive study. The male:female ratio was 1:2, and the
age ranged from 22 to 97 years with a mean ± (standard deviation [SD]) age of 57.91 ± 12.0 years, there was no statistically significant difference between the mean ages of the men 58.8 (12.4) and women 57.5 (11.8) studied (t-test = 0.213; P = 0.552). A total of 146 patients (28.4%) were aged 65 years and above. Regarding the educational status of the population, 172 (33.5%) had tertiary education representing the largest group.

The mean (SD) duration of diagnosis of hypertension in the 514 patients was 7.8 (7.9) years, (range: 1 month–40 years) while they had been receiving treatment for a mean (SD) duration of 7.4 (7.8) years (range: 2 weeks–36 years).

Only 16 (3.1%) patients were currently smoking and 67 (13%) admitted to social use of alcohol. Fifty percent (254) of the patients had comorbidities, with 85% having one comorbidity only and 14.2%, 0.8% having two and three, respectively. The different comorbidities as documented in the case records were mainly diabetes mellitus 131 (25.5%), osteoarthritis 78 (15.2%), obesity 16 (3.1%), and peptic ulcer disease 15 (2.9%) among others.

### Antihypertensive medicines prescribed

A total of 67 (13%) patients were on one antihypertensive medicine (monotherapy), of which 11/67 (16.4%) of them had only antihypertensive medicine prescribed, whereas the other 56/67 (83.6%) had other medicines besides antihypertensive medicines. Four hundred and forty-seven (87%) were on combination therapy of two or more antihypertensive medicines, (combination therapy). In the patients on combination therapy, 142 (27.63%), 137 (26.63%), 113 (21.98%), and 55 (10.70%) of them had 2, 3, 4, and 5 or more antihypertensive medicines prescribed.

CCBs were the most prescribed class of antihypertensive medicines 362 (70.4%) and alpha-blockers the least prescribed group 9 (1.8%). Beta-blockers 118 (23.0%) and alpha-blockers - 9 (1.8%) were prescribed only in combination therapy. The most common combinations of antihypertensive medicines were diuretics and CCBs. In patients using only one antihypertensive medicine, more patients were on ACEI 31 (46.3%), and this was closely followed by CCB at 26 (38.8%), other medicines used include ARB 5 (7.5%), centrally acting medicine 3 (4.5%), and diuretics 2 (3.0%).

### Adverse drug reactions experienced

Ninety-three (18.1%) patients experienced an ADR to their antihypertensive medicines. Using the causality assessment scales to classify the probability of the adverse reactions, with WHO assessment[19] 29 (31.2%), had their adverse reactions classified as probable and 56 (60.2%) as possible. However, 7 (7.5%) and 1 (1.1%) patient(s) had experienced adverse reactions judged as being unlikely and conditional, respectively.

Using the Naranjo assessment algorithm[20] to assess the adverse reactions, 55 (59.1%) were classified as having had a possible adverse reaction, 37 (39.8%) were probable, and 1 (1.1%) was doubtful.

ADRs increased with increase in the number of antihypertensive medicines, and it was statistically significant [Table 1].

Proportionately, more men 35/174 (20.1%) than women 58/340 (17.1%) reported an adverse reaction to their antihypertensive medications, but it was not statistically significant ($\chi^2 = 0.725$, df = 1, $P = 0.39$). Elderly patients 20/146 (13.7%) reported fewer ADR compared to younger patients 73/368 (19.8%), although it was not significant. ($\chi^2 = 2.658$. df = 1. $P = 0.103$).

### Profile of adverse reactions reported

Dry cough was present in 15/24 (62.5%) of those who had an adverse reaction to ACEI, and a patient had passage of loose stools, excessive micturition was seen in 19/26 (73.1%) of the patients on diuretics, while 11/25 (44%) of the patients on CCB (either as monotherapy or in combination) complained of increased frequency of micturition to their medicines distinct from an increase in volume (polyuria) seen with diuretics. The reactions are also documented in Table 2. The system organ classification is shown in Table 3, renal and urinary disorders being the most commonly reported system. Following the development of adverse reactions in these 93 patients, 46 of them (49.5%) discontinued their medicines with five of them substituting with another brand while 30 (32.2%) reduced their doses; however, 17 (18.3%) took no action [Table 2].

### Adverse reactions: Symptoms checklist

With the administration of a modified symptom checklist to determine drug-related symptomatology in all the patients, 405 (78.8%) had adverse reactions related to the use of their medications. The frequency of micturition, poor erection, headaches, and reduced sexual urge were the symptoms most related to drug use with 37.7%, 25.7%, 22.6%, and 21.2%, respectively. The frequencies of the other symptoms are elucidated in Table 4.

Serious adverse reactions: Notable in this outpatient-based study was the absence of serious adverse reactions as there were no deaths, hospitalizations, disabilities, or life-threatening events that required intervention to prevent permanent damage.

### Discussion

There is a need to define the present profile of antihypertensive medicines by finding out the present pattern of ADR which

| Table 1: Distribution of the number of antihypertensive medicines used by the 514 patients and frequency of adverse reactions experienced |
|--------------------------------------------------|
| **Antihypertensive medicine** | **Number of patients** | **ADR experienced, n (%)** |
|-------------|-----------------|-----------------|
| 1 | 67 | 10 (14.9) |
| 2 | 142 | 18 (12.7) |
| 3 | 137 | 21 (15.3) |
| 4 | 113 | 32 (28.3) |
| ≥5 | 55 | 12 (21.8) |

$\chi^2=12.460$, df=4, $P=0.014$ (significant). ADR=Adverse drug reaction.
The patients who used diuretics complained about the probability as this expands the database of ADRs. The frequency of ADRs appeared to be higher in males, although the use of their medicines and cannot recall on questioning. Different studies have used this method though modified in this study; it also showed that a high proportion of patients had symptoms that they attributed to their medicines. The frequency of erectile dysfunction reported was more following the use of the symptom checklist. Many patients attribute sexual dysfunction to their antihypertensive medicines, therefore adherence to these medicines may be poor due to their perceived adverse effect. Assessing the frequency of this complaint using a checklist or questionnaire has been shown to be helpful. It may have also contributed albeit indirectly to more males reporting adverse reactions on direct questioning. The proportion of patients who had ACEI induced cough in this study was higher than shown in other studies. The patients who used diuretics complained of excessive micturition; this had a serious impact on the patient’s therapy as diuretics accounted for the highest number of reactions reported. The excessive micturition seen with diuretics may be due to the dose of diuretics, especially hydrochlorothiazide available in this environment. A study carried out in the North Central part of Nigeria also showed diuretics accounting for the highest rate of discontinuations to therapy. Of interest were the reports of increased frequency of micturition following the use of CCBs. As distinct from the excessive micturition with diuretics, the CCB account for increased frequency (number of times) not reflected in the volumes of urine passed. This was observed early following the introduction of the CCBs. This finding need to be further investigated as it was also seen using the MedDRA system organ classification that the renal and urinary disorders had the highest frequency. We equally note the development of dizziness and dryness of legs to alpha blockers, (though infrequently used in this study) two of the users (22%) had adverse reactions, the reactions observed may be related to the orthostatic hypotensive effect of alpha blockers.

Noticeable in this study, was the absence of reports of ADR to the ARBs. A reduced frequency has also been seen in another study by Lip and Beevers. The medicine induced symptom checklist was to improve the reporting of patients who may have symptoms associated with the use of their medicines and cannot recall on questioning. Different studies have used this method though modified in this study; it also showed that a high proportion of patients had symptoms that they attributed to their medicines.

### Table 2: Adverse reactions experienced by patients to antihypertensive medicines and actions taken by the patients following the reactions

| Frequency of medicine class | Adverse reactions experienced (n) | Frequency (%) | Action was taken by patients |
|----------------------------|----------------------------------|---------------|-----------------------------|
| Calcium channel blockers (n=362) | Frequent micturition - 11, dizziness - 5, headaches - 5, others - 10 | 25/362 (6.9) | De - 10, reduced dose - 11, none - 4 |
| Angiotensin converting enzyme inhibitors n=278 | Dry cough - 15, dizziness - 2, diarrhoea, abdominal pain - 2, others - 5 | 24/278 (8.6) | De - 14, reduced dose - 6, none - 4 |
| Diuretics (n=273) | Excessive micturition - 19, dizziness - 5, headaches - 3, others - weakness, insomnia | 26/273 (9.5) | De - 14, reduced dose - 9, none - 4 |
| Beta blockers (n=118) | Dizziness - 1, dry lips - 1, cramps in foot - 1, abnormal sensation in head - 1 | 4/118 (3.4) | De - 1, none - 3 |
| Centrally acting (n=95) | Dizziness - 4, headaches - 3, weakness - 5, others - 5 | 12/95 (12.6) | De - 7, reduced dose - 2, none - 2 |
| Alpha blockers (n=9) | Dizziness - 1, dryness of legs - 1 | 2/9 (22.2) | Reduced dose - 2 |

**MedDRA=Medical Dictionary for Regulatory Activities**

### Table 3: The system organ classifications (Medical Dictionary for Regulatory Activities) of the reported adverse reactions by the hypertensive patients

| System organ classification (MedDRA) | Frequency (n) |
|-------------------------------------|---------------|
| Renal and urinary disorders         | 32            |
| Respiratory, thoracic and mediastinal disorders | 16 |
| Nervous system disorders            | 17            |
| General disorders and administration site conditions | 12 |
| Cardiac disorders                   | 12            |
| Gastrointestinal disorders          | 5             |
| Reproductive system and breast disorders | 5 |
| Musculoskeletal and connective tissue disorders | 2 |
| Skin and subcutaneous disorders     | 2             |
| Eye disorders                       | 1             |
| Psychiatric disorders               | 1             |

The use of the medicine induced symptom checklist was to improve the reporting of patients who may have symptoms associated with the use of their medicines and cannot recall on questioning. Different studies have used this method though modified in this study; it also showed that a high proportion of patients had symptoms that they attributed to their medicines. The frequency of erectile dysfunction reported was more following the use of the symptom checklist. Many patients attribute sexual dysfunction to their antihypertensive medicines, therefore adherence to these medicines may be poor due to their perceived adverse effect. Assessing the frequency of this complaint using a checklist or questionnaire has been shown to be helpful. It may have also contributed albeit indirectly to more males reporting adverse reactions on direct questioning. The proportion of patients who had ACEI induced cough in this study was higher than shown in other studies. The patients who used diuretics complained of excessive micturition; this had a serious impact on the patient’s therapy as diuretics accounted for the highest number of reactions reported. The excessive micturition seen with diuretics may be due to the dose of diuretics, especially hydrochlorothiazide available in this environment. A study carried out in the North Central part of Nigeria also showed diuretics accounting for the highest rate of discontinuations to therapy. Of interest were the reports of increased frequency of micturition following the use of CCBs. As distinct from the excessive micturition with diuretics, the CCB account for increased frequency (number of times) not reflected in the volumes of urine passed. This was observed early following the introduction of the CCBs. This finding need to be further investigated as it was also seen using the MedDRA system organ classification that the renal and urinary disorders had the highest frequency. We equally note the development of dizziness and dryness of legs to alpha blockers, (though infrequently used in this study) two of the users (22%) had adverse reactions, the reactions observed may be related to the orthostatic hypotensive effect of alpha blockers.
Table 4: Frequency of symptoms attributed to medicine use in the 514 hypertensive patients using the modified symptoms checklist

| Symptom                           | n (%)   |
|----------------------------------|---------|
| Frequency of micturition         | 190 (37.0) |
| Poor erection                    | 65 (25.7) |
| Headache                         | 116 (22.6) |
| Reduced sexual urge              | 109 (21.2) |
| Insomnia                         | 95 (18.5) |
| Weakness                         | 95 (18.5) |
| Nightmares (bad dreams)          | 82 (16.0) |
| Coughing                         | 79 (15.4) |
| Fatigue/little initiative        | 74 (14.4) |
| Swollen ankles/oedema            | 71 (13.8) |
| Muscular cramp/myalgia           | 70 (13.6) |
| Dizziness upon standing up       | 65 (12.6) |
| Palpitation                      | 60 (11.7) |
| Warm feeling/flushes in the face | 55 (10.7) |
| Dryness of mouth                 | 45 (8.8)  |
| Impotence                        | 13 (7.3)  |
| Other dizziness (unrelated to posture) | 35 (6.8)  |
| Disturbance of taste             | 25 (4.9)  |
| Constipation                     | 20 (3.9)  |
| Depressed                        | 20 (3.9)  |
| Rash/itching                     | 19 (3.7)  |
| Nausea                           | 19 (3.7)  |
| Dyspnœa                          | 17 (3.3)  |
| Cold hands/feet                  | 15 (2.9)  |
| Urinary incontinence             | 11 (2.1)  |
| Nervous/restless                 | 9 (1.8)   |
| Diarrhoea                        | 6 (1.2)   |

Some knowledge of the profile of antihypertensive medicines in use by the physicians will aid the management of hypertension. Further studies are required to characterize this problem.

Conclusions

In all, there is a relatively high prevalence of adverse reactions experienced by patients on antihypertensive therapy resulting in a high rate of discontinuations as seen in this study. Notable reactions experienced by the patients include dry cough to ACEIs, excessive micturition to diuretics, and frequent micturition in patients on CCBs. Utilization of a medicine induced symptom checklist revealed symptoms which were not reported on direct questioning such as reduced libido and erectile dysfunction.

Some knowledge of the profile of antihypertensive medicines in use by the physicians will aid the management of hypertension. Further studies are required to characterize this problem.

Acknowledgments

We would like to thank the University of Benin Teaching Hospital management and members of staff of the Department of Medicine and the consultant outpatient department for their assistance. We would also like to thank the patients who participated in this study. This study was self-funded and there are no potential conflicts of interest.

References

1. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2224-60.
2. Adeloye D, Basquill C, Aderemi AV, Thompson JY, Obi FA. An estimate of the prevalence of hypertension in Nigeria: A systematic review and meta-analysis. J Hypertens 2015;33:230-42.
3. Sytkowski PA, D’Agostino RB, Belanger AJ, Kannel WB. Secular trends in long-term sustained hypertension, long-term treatment, and cardiovascular mortality. The Framingham Heart Study 1950 to 1990. Circulation 1996;93:697-703.
4. Opie LH, Seedat YK. Hypertension in sub-Saharan African populations. Circulation 2005;112:3562-8.
5. Salako BL, Ogah OS, Adebiyi AA, Adedapo KS, Bekibele CO, Oluleye TS, et al. Unexpectedly high prevalence of target-organ damage in newly diagnosed Nigerians with hypertension. Cardiovasc J Afr 2007;18:77-83.
6. Neal B, MacMahon S, Chapman N, Cutler J, Fagard R, Whelton P, et al. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overview of randomised trials. Lancet 2000;356:1955-64.
7. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr., et al. Seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003;42:1266-52.
8. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs. diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2981-97.
9. Ross SD, Akhras KS, Zhang S, Rozinsky M, Nalysnyk L. Discontinuation of antihypertensive drugs due to adverse events: A systematic review and meta-analysis. Pharmacotherapy 2001;21:940-53.
10. SoRelle R. Withdrawal of Posicor from market. Circulation 1998;98:831-2.
11. Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, et al. Adverse drug events in ambulatory care. N Engl J Med 2003;348:1556-64.
12. Aronson JK. Adverse drug reactions – No farewell to harms. Br J Clin Pharmacol 2007;63:131-5.
13. Isah A, Isah E, Shah D, Obasohan A. An assessment of patient’s knowledge and experience in a Nigerian Teaching Hospital Hypertension Clinic. Niger Postgrad Med J 1998;5:173-5.
14. Bland JM, Butland BK, Peacock JL, Poloniecki J, Reid F, Sedgwick P. Sample size calculation. In: Statistics Guide for Research Grant Applicants. London: St. George’s University of London; 2012. p. 37-44. Available at: https://www-users.york.ac.uk/~mb55/guides/ guide14.pdf [Last cited on 2016 Nov 28].
15. Ouwubere B, Kadiri S, editors. Guidelines for the Management of Hypertension in Nigeria. 2nd ed. Enugu: Ezu Books Limited; 2005.
16. Bulpitt CJ, Dollery CT. Side effects of hypotensive agents evaluated by a self-administered questionnaire. Br Med J 1973;3:485-90.
17. Olsen H, Klemetsrud T, Stokke HP, Tretli S, Westheim A. Adverse drug reactions in current antihypertensive therapy: A general practice survey of 2586 patients in Norway. Blood Press 1999;8:94-101.
18. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf 1999;20:109-17.
19. WHO-UMC. The Use of the WHO-UMC System for Standardised Case Causality Assessment; 2012. Available from: http://www.who-umc.org/graphics/26649.pdf. [Last cited on 2015 Jun 12].
20. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
21. Lip GY, Beevers DG. Doctors, nurses, pharmacists and patients – The Rational Evaluation and Choice in Hypertension (REACH) survey of hypertension care delivery. Blood Press Suppl 1997;1:6-10.
22. Düssing R. Adverse events, compliance, and changes in therapy. Curr Hypertens Rep 2001;3:488-92.
23. Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or casual? The role of causality assessment in pharmacovigilance. Drug Saf 1997;17:374-89.
24. Rodenburg EM, Stricker BH, Visser LE. Sex differences in cardiovascular drug-induced adverse reactions causing hospital admissions. Br J Clin Pharmacol 2012;74:1045-52.
25. Vandenbroucke MJ, Evans SJ, Kelly BJ, Bradshaw F, Currie WJ, Cooper WD. Factors affecting the reporting of symptoms by hypertensive patients. Br J Clin Pharmacol 1984;18 Suppl 2:189S-95S.
26. Curb JD, Borhani NO, Blaszkowski TP, Zimbaldi N, Fotiu S, Williams W. Long-term surveillance for adverse effects of antihypertensive drugs. JAMA 1985;253:3263-8.
27. Prisant LM, Carr AA, Bottini PB, Solursh DS, Solursh LP. Sexual dysfunction with antihypertensive drugs. Arch Intern Med 1994;154:730-6.
28. Salami A, Katibi I. Angiotensin converting enzyme inhibitors associated cough a prospective evaluation in hypertensives. Ann Afr Med 2005;4:118-21.
29. Ajayi AA, Adigun AQ. Angioedema and cough in Nigerian patients receiving ACE inhibitors. Br J Clin Pharmacol 2000;50:81-2.
30. Katibi IA, Olarinoye JK. Antihypertensive therapy among hypertensive patients as seen in the middle belt of Nigeria. Ann Afr Med 2004;3:177-80.
31. Isah A, Obasohan A, Oyewo E, Obaju-Obodo J. Amlodipine versus nifedipine in the treatment of mild-to-moderate hypertension in black Africans. Curr Ther Res 1996;57:300-8.
32. Kamaruzzaman S, Watt H, Carson C, Ebrahim S. The association between orthostatic hypotension and medication use in the British Women’s Heart and Health Study. Age Ageing 2010;39:51-6.
33. Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. Am J Cardiol 1995;75:793-5.