# Impact Of Clinical Pharmacist-Led Structured Medication Review Services On Treatment Outcomes On Hypertensive Patients: A Pilot Study

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#### Abstract:

Background: Hypertension, a leading cause of morbidity and mortality in adults aged  $\geq 20$  years, causes an estimated 7.5 million deaths globally and also the leading cause of disability and mortality among adults in rural and urban communities in Nigeria. Half of people with hypertension have uncontrolled blood pressure due to poor treatment outcomes. The remunerations of uncontrolled hypertension can be fatal. Little is actually known of clinical pharmacist-led interventions in chronic disease management.

Aim: The overall aim of the study was to evaluate the impact of pharmacist-led Structured Medication Review Services on treatment outcomes on hypertensive patients in a secondary health facility in Jos, Plateau State, Nigeria.

Methods: A non-randomized one site controlled study of 51 hypertensive patients  $aged \ge 20$  years was carried out for 1 month at the Dadin Kowa Comprehensive Health Center, a secondary health facility located in Jos, Plateau State, Nigeria. Data was collected by using a Structured Medication Review Service questionnaire which was divided into four sections: patients' demographics, clinical characteristics, medication adherence level and health-related quality of life. The intervention focused mainly on educational and medication and adherence counseling directly to the patient. The main outcome measure for this analysis was the measure of systolic blood pressure (SBP), diastolic blood pressure (DBP), BP control and health-related quality of life.

Results: Among the hypertensive patients, mean reduction in blood pressure pre- and post-intervention was SBP [146.6  $\pm$  17.62 to 137.7  $\pm$  17.37 (p=0.001)], DBP [88.80  $\pm$  2.41 to 85.80  $\pm$  2.92 (p = 0.003)]. In this study, the intervention showed a significant blood pressure control and reduction of systolic blood pressure after pharmacist mediated patient education and counseling. At baseline measurement, majority of the participants had low-adherence. Post-intervention showed the health-related quality of life physical composite score versus mental composite score (48.67%: 52.67%). This indicated an average health-related quality of life among the study participants.

Conclusion: Clinical Pharmacist-led Structured Medication Review Services through proper patient-education with medication and adherence counseling have demonstrated a significant impact in greatly improving blood pressure treatment outcomes and accordingly improved participants' clinical and humanistic outcomes, stimulating them to have a positive physical and mental state of health.

Keywords: Blood Pressure, Clinical Pharmacist, Hypertension, Medication Adherence, quality of life

## I. INTRODUCTION

Hypertension, a leading cause of morbidity and mortality in adults aged  $\geq 20$  years, causes an estimated 7.5 million deaths globally (World Health Organization [WHO], 2015). A greater portion of this burden is borne by low- and middleincome countries in contrast to high-income countries, which have experienced a decrease in hypertension (WHO, 2014). Hypertension is often detected at routine check-up or when a patient present with complications resulting from long-term uncontrolled blood pressure (Ataklte, Erqou, Kaptoge, Taye, Echouffo-Tcheugui, & Kengne, 2015). Findings have shown that a 10% relative reduction in elevated blood pressure and premature mortality from hypertension is possible if risk factor targets for reduced salt intake, diabetes, obesity, alcohol and tobacco use are achieved (Oyebode, Oti, Chen, & Lilford, 2016; WHO, 2016). In Nigeria, hypertension ranks first among the non-communicable diseases (Okwuonu, Ojimadu, Okaka, & Akemokwe, 2014) with a prevalence of 8% - 46.4 % in adults in both rural and urban communities. The burden of hypertension in Nigeria has increased with time in an increasing adult population and changing lifestyle, with many persons suffering from the clinical complications of hypertension and decreased Health-related quality of life (Okwuonu et al., 2014).

Findings have shown that more than half of people with hypertension have uncontrolled blood pressure (Gwadry-Sridhar et al., 2013). A significant cause of uncontrolled blood pressure is poor medication adherence (Mills et al., 2016). About 43% to 65.5% of hypertensive patients have poor medication-adherence (Mills et al., 2016) thus are at greater risks for coronary disease, cerebrovascular disease, and chronic heart failure. The remunerations of uncontrolled hypertension can be fatal. Many Nigerian lives could be saved if clinical pharmacist services were introduced to improve treatment outcomes. In the current study, treatment outcomes included blood pressure control, and health-related quality of life.

The general aim of the pilot study was to evaluate the impact of clinical pharmacist-led structured medication review services on treatment outcomes on hypertensive patients in a secondary health facility in Jos, Plateau State, Nigeria. The specific objectives of the study: 1. To compare mean blood pressure reduction pre- and post-intervention, 2. To assess medication-adherence at pre-intervention. 3. To assess health-related quality of Life at post-intervention.

# II. METHODOLOGY

A non-randomized one site controlled study was carried out for 1 month at the Dadin Kowa Comprehensive Health Center, a secondary health facility located in Jos, Plateau State, Nigeria. Based on inclusion criteria (out-patients diagnosed with hypertension of either sex, taking an antihypertensive medication for about one month, aged  $\geq 20$ years), a total of 51 patients were enrolled after obtaining ethical approval from the Plateau State Hospital Management Board. Informed consent was also obtained from participants. Data was collected by using a Structured Medication Review Service questionnaire which was divided into four sections: demographics, clinical characteristics (blood patients' pressure, comorbidities, laboratory parameters), medication adherence level and health-related quality of life. Structured Medication Review Service is defined as a critical examination of a patient's medication (s) by a clinical pharmacist in collaboration with other health professionals, with the objectives of reaching an agreement with the patient about their treatment, improving treatment outcomes, minimizing the number of medication-related problems and

avoiding wastage (Fernández-Llamazares et al., 2012). Structured medication review services are a distinct group of services that improve treatment outcomes for individual patient with chronic medical conditions (Bluml, 2005) and are a care model built on team-based care principles that are effective in optimizing treatment outcomes (Santschi et al., 2014). The Structured Medication Review Services are distinct from Standard Medication Dispensing Practices and focus on a patient-centered process of care in improving treatment outcomes and detecting, resolving, and preventing medication-related problems.

Hypertension refer to systolic blood pressure  $\geq 140$  mmHg and diastolic blood pressure  $\geq 90$  mmHg at the time of the study or antihypertensive therapy for at least 30 days prior to the study (James et al., 2014). Hypertension is considered to be controlled in all treated hypertensive patients who had a systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg at the time of the study. Blood pressure was measured in participants in a sitting position after at least 5 minutes of rest (James et al., 2014). Blood pressure was measured using an electronic blood pressure monitoring type OMRON<sup>®</sup> HEM – 720 – E. Mean blood pressure reduction was achieved from mean blood pressure pre- and post-intervention. Body weight was measured in kilogram (Kg) to the nearest 0.1 kg using a PH – 2015A brand electronic weight scale.

Adherence was measured using Morisky Medication Adherence 4-Item Scale (MMAS-4), a 4-item questionnaire with 4 yes/no questions with a scoring scheme of "Yes" = 0and "No" = 1 Adherence was rated as follows: high adherence (=4), medium adherence (3), low adherence (< 2). For the purpose of the current study, higher adherence score indicates better adherence. Due to the size of the sampled population, all patients who had adherence level ( $\leq 2$ ) were considered as low-adherent. Another validated tool. the Short Form-12 version 2 (SF-12 v. 2.0), was used to assess health-related quality of life post-intervention. The SF-12 described the physical composite health and mental composite health measures of individual patient (Ware et al., 1995). Physical and Mental Health Composite Scores (PCS & MCS) are computed using the scores of twelve questions and range from 0 to 100, where a zero score indicates the lowest level of health measured by the scales and 100 indicates the highest level of health. Individuals with a physical and mental composite health scores of  $\geq 48.0$  were considered average or above average health. Scores below 48.0 were considered poor health status. Intervention or patient counselling started immediately at baseline with subsequent weekly follow-ups by visits at clinic or through short-message-service (SMS) and phone calls. The intervention was in the form patient education, counselling on medication and lifestyle adherence and blood pressure control. The impact of clinical pharmacist intervention was assessed based on mean blood pressure reduction obtained pre- and post-intervention. Dichotomous variables gathered were analyzed by descriptive frequency while pharmacists impact on blood pressure was analyzed by paired t-test using statistical package for social sciences (SPSS version 25). Level of significance was  $P \leq 0.005$ . Main outcome measures were the measure of systolic blood pressure (SBP), diastolic blood pressure (DBP), blood pressure reduction and health-related quality of life using a validated questionnaire assessed at pre- and post-intervention.

#### **III. RESULTS**

A total of 51 hypertensive patients were recruited in the pilot study. There were 23 (45.1%) males and 28 (54.9%) females. The minimum and maximum ages were 28 years and 89 years respectively. The mean age  $\pm$  SD of participants was  $52.9 \pm 12.5$  years. The mean  $\pm$  SD weight of participants was  $70.0 \pm 16.45$ . The socio-demographic characteristics of participants were given (Table 1.0). Frequencies of comorbidities and frequently prescribed antihypertensive medications were given (Table 2.0). The mean blood pressure reductions pre- and post-intervention were SBP 8.9 mmHg and DBP 3.0 mmHg as demonstrated (Table 3.0). At baseline, participants' adherence level was measured (Table 4.0). The total adherence score was 2.41. The SF-12 V. 2.0 healthrelated quality of life was determined with a physical composite score of 48.67 and a mental composite score of 52.67 (Table 5.0).

VARIBLE	RESPONSE	FREQUENCY	PERCENTAGE
SEX (n=51)	Male	23	45.1
	Female	28	54.9
Educational	No formal	9	18.4
status (n=49)			
	Primary	4	8.2
	Secondary	18	36.7
	Tertiary	18	36.7
Marital status	Married	46	93.9
(n=49)			
	Single	3	6.1
Occupational	No formal	1	2.4
status			
	Public	2	4.6
	servant		
	Civil servant	17	40.5
	Business	12	52.4
Non-smoker	Yes	49	98
Family	Yes	29	59.2
history of			
hypertension			
Lack of	Yes	27	52.9
purposeful			
exercise			
Alcohol	Yes	40	81.6
intake			
Caffeine	Yes	38	74.5
intake			
Frequent visit	Yes	37	72
to physician's			
office			
Living alone	Yes	45	88.2

Source: Socio-demographic details of hypertensive patients at pre-initiation of the Structured Medication Review Services at the Dadin Kowa Comprehensive Health Center, Jos, Plateau State

Table 1: Socio-Demographic Details of Respondents				
VARIABLE	FREQUENCY	PERCENT (%)		
Frequently prescribed anti-hypertensives				
Amlodipine	35	37.6		
Moduretic	19	20.4		
Hydrochlorothiazide	17	18.3		

Lisinopril Atenolol	12 10	12.9 10.8	
<b>Co-morbidities of hypertensive patients</b>			
Diabetes mellitus	10	20.4	
Peptic ulcer disease	3	6.1	
Source: Most frequently prescribed anti-hypertensives and co-			

morbidities of hypertensive patients at the Dadin Kowa Comprehensive Health Center in Jos, Plateau State, Nigeria.

Table 2: Frequently Anti-Hypertensives and Co-Morbidities			
VARIABLE	MEAN ± SD	CORRELATION	95 % CI:
			<b>P</b> ≤ 0. 005
SBP [On	146. $6 \pm 17.62$	0.853	0.001
Enrolment]			
SBP [Follow-	$137.7 \pm 17.37$		
Up]			
DBP [On	$88.8 \pm 2.4$	0.406	0.003
Enrolment]			
DBP [Follow-	$85.8 \pm 2.9$		
Up]			

Source: Mean blood pressure reductions of participants preand post-intervention at the Dadin Kowa Comprehensive Health Care Center in Jos, Plateau State from May to June, 2019. SBP = Systolic Blood Pressure, DBP = Diastolic Blood Pressure

VARIABLE	RESPONSE	FREQUENCY	PERCENT (%)
Do You Sometimes	Yes	25	49
Forget to take your			
high blood			
pressure medicines			
	No	25	51
Due to one reason or	Yes	21	42
another, did you even	r		
have problems			
remembering to take	;		
your high blood			
pressure medicines			
-	No	29	58
When You Felt	Yes	24	47
Better, did you			
sometimes			
Stop Taking Your			
high blood pressure			
medicines?			
	No	27	53
When You Felt	Yes	15	29
Worse/Sick, did you			
sometimes stop			
taking your high			
blood pressure			
medicines?			
	No	36	70
	ADHERENCE		
	EQUENCY	PERCENT	(%)
Non	29	56.9	
adherence			
Low	12	23.5	
adherence			
Medium	6	11.8	
adherence			
High	4	7.8	
adherence			

Source: Medications Adherence score pre-intervention results among hypertensive patients at the Dadin Kowa Comprehensive Health Center in Jos, Plateau State in 2019

Table 4: Adherence Level of Participants $(n=51)$			
VARIABLE	RESPONSE	FREQUENCY	PERCENT
			(%)
General Health	Good	38	74.5
Limited in	Does not limit	37	72.0
moderate	at all		
activities			
Limited in	Does not limit	33	64.0
walking a	at all		
distance or			
climbing a flight			
of stairs			
Accomplished	A little of the	17	33.3
less than you	time		
would like			
Limited in kind	A little of the	19	37.3
of work	time		
Bodily pain	A little bit of	25	49.0
	the time		
Time with lot of	Most of the	22	43.1
energy	time		
Problems with	A little of the	20	39.0
regular activities	time		
due to sadness or			
worries			
Trouble in	Most of the	17	33.3
concentration	time		
doing your			
regular work			
Time felt calm	Some of the	20	39.2
and peaceful	time		
Time felt sad	Some of the	19	37.3
and down	time		$\mathbf{X}$
Physical health	None of the	31	60.8
or emotional	time		
problems			· · · · · · · · · · · · · · · · · · ·
interfered with			
your social			
activities			

Source: Participants' responses to various items in each scale post-intervention among hypertensive patients at the Dadin Kowa Comprehensive Health Center in Jos, Plateau State in 2019

Table 5: Health-Related Quality of Life of Participants

# IV. DISCUSSION

Assessing quality of life and medication adherence level help in evaluating the physical and mental health of hypertensive patients. In this pilot study conducted among 51 adult hypertensive patients attending follow-up treatment at the Dadin Kowa Comprehensive Health Center in Jos, Nigeria, there were more female participants than males. The current study showed that most of the participants were married and had at least secondary or tertiary certificate. In agreement to the current study, a study reported that the prevalence of hypertension increases among postmenopausal women due to loss of estrogen production (Poornima, et al., 2014) and with body mass index [Renu, Meenal, & Satwanti, 2015). The greater portion of secondary or tertiary educated participants could be due to the situation wherein most urban dwellers in many African cities were opportune to obtain tertiary education and job-liberties that city dwellers have (Agyemang, 2006).

Majority of the participants had a family history of hypertension, non-smokers and most of them lack purposeful exercise. Familial history is recognized to be one of the risk factors for essential hypertension (Ferrari et al., 2004). The non-smoking could be due to participants' religious beliefs that prohibits smoking or health awareness education that described the dangers of smoking to the public. The lack of exercise by many respondents could be due to urban lifestyle where many urban dwellers have long hours of work or physical inactivity. This is in agreement with Lemogoum et al. (2017). Anti-hypertensives were prescribed in managing this long-term condition. This correlates with evidence from clinical trials demonstrating that blood pressure lowering with antihypertensive medications is associated with significant reductions in cardiovascular mortality and disability (M'Buyamba-Kabangu et al., 2013; Elmer et al., 2006; Lewington, et al., 2002). Anti-hypertensive medication treatment is a bed-rock in lowering blood pressure, where bulk of the patients often have need of  $\geq 2$  anti-hypertensive medications to achieve blood pressure targets of < 140/90mmHg in general or < 130/80 mmHg in patients with diabetes (Kesarwani et al., 2009).

Among the hypertensive patients, mean reduction in blood pressure (SBP 146.6  $\pm$  17.62 to 137.7  $\pm$  17.37, DBP 88.80  $\pm$  2.41 to 85.80  $\pm$  2.92) was observed from baseline to final follow-up. In this study, the intervention showed a significant reduction of systolic blood pressure after pharmacist mediated patient education and counseling. Previous studies also showed similarities with the results of the current study (Adel, Soad, & Hameed, 2014; USCDC, 2016).

At baseline, only 7.8% and 11.8% of participants had high and medium medication adherence levels respectively. Majority of the participants were classified as non-adherent in the current study. This high percent of low adherence was due to participants who often forgot to take their anti-hypertensive medications. Previous studies have also produced similar findings of patients' adherence level to anti-hypertensive medications (Liwa et al., 2017; Irvin et al., 2012). Medication adherence can improve when clinical pharmacists are included as key members of the healthcare team (Santschi et al., 2014; Carter et al., 2010).

Self-reported health-related quality of life measures present a component of subjectivity into health status measurement, which is useful in providing a more 'patientcentered' view of their health. These measures are grounded on a person's perception of their health status and wellbeing. The results of this study demonstrated that at postintervention, general health perception had the highest health related quality of life (HRQOL) score, implying that most of the patients could perform various physical activities in their respective lives, although a small number had difficulties climbing several flight of stairs or walking more than one mile and running. This is as a result of many participants reporting mild to moderate bodily pain occurring in the knee, waist, stomach or chest. They however had a good mental health status with most of them performing their normal social activities without much hindrance. These findings then suggest that hypertensive patients displayed a poorer healthrelated quality of life especially in their physical functioning with more reports of bodily pain than those subjects without hypertension.

## V. CONCLUSION

Clinical pharmacists possess important clinical skills and knowledge that improve treatment outcomes among patients with hypertension. Clinical pharmacist-led Structured Medication Review Services through proper patient-education, medication and adherence counseling have demonstrated a significant impact on greatly improving hypertension treatment outcomes and accordingly improving participants' clinical and humanistic outcomes, stimulating them to have a positive physical and mental state of health.

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# REFERENCES

- [1] Adel, A.W., Soad, H., & Hameed, D. (2014). "Effect of lifestyle intervention program on controlling hypertension among older adults." J Educ Pract, 5 (5), 61-71.
- [2] Ataklte, F., Erqou, S., Kaptoge, S., Taye, B., Echouffo-Tcheugui, J.B., & Kengne, A.P. (2015). Burden of undiagnosed hypertension insub-Saharan Africa: a systematic review and meta-analysis. Hypertension, 65, 291–298.
- [3] Bluml, B.M. (2005). Definition of medication therapy management: development of profession wide consensus. Journal of American Pharmacy Association, 45 (5), 566– 72.
- [4] Carter. B.L., Clarke, W., Ardery, G., Weber, C.A., James, P.A., Vander Weg, M., et al. (2010). A clusterrandomized effectiveness trial of a physician-pharmacist collaborative model to improve blood pressure control. Circ Cardiovascular Quality Outcomes, 3 (4):418–23.
- [5] Elmer, P.J., Obarzanek, E., Vollmer, W.M., et al. (2006). PREMIER Collaborative Research Group. Effect of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. Ann Intern Med, 144, 485– 495.

- [6] Ferrari, P., Hess, L., Pechere-Bertschi, A., Muggli, F., & Burnier, M. (2004). Reasons for not intensifying antihypertensive treatment (RIAT): a primary care antihypertensive intervention study. J Hypertens, (6), 1221-20.
- [7] Gwadry-Sridhar, F.H., Manias, E., Lal, L., Salas, M., Hughes, D.A., Ratzki-Leewing, A., & Grubisic, M. (2013). Impact of Interventions on Medication Adherence and Blood Pressure Control in Patients with Essential Hypertension: A Systematic Review by the ISPOR Medication Adherence and Persistence Special Interest Group. International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Elsevier, 16, 863 – 871.
- [8] James, P.A., Oparil, S., Carter, B.L., Cushman, W.C., Dennison-Himmelfarb, C., Handler, J., Lackland, D.T., LeFevre, M.L., MacKenzie, T.D., Ogedegbe, O., Smith Jr, S.C., Svetkey, L.P., Taler, S.J., Townsend, R.R., Wright Jr, J.T., Narva, A.N., Ortiz, E. (2014). Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). Journal of American Medical Association, 311 (5), 507-520. doi:10.1001/jama.2013.284427 Published online December 18, 2013.
- [9] Kesarwani, M., Perez, A., Lopez, V.A., Wong, N.D., & Franklin, S.S. (2009). Cardiovascular comorbidities and blood pressure control in stroke survivors. J Hypertens, 27 (5), 1056-63.
- [10] Lemogoum, D., Ngatchou, W., Janssens, C., et al. (2012).Effects of hunter-gatherer subsistence mode on arterial distensibility in Cameroonian pygmies. Hypertension, 60,123–128.
- [11] Lewington, S., Clarke, R., Qizilbash, N., et al. (2002). Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet, 360, 1903–1913.
- [12] Liwa, A., Roediger, R., Jaka, H., Bougalia, A., Langwick, S.A., Smart, L.R., & Peck, R. (2017). Herbal and alternate medicine use in Tanzania adults admitted with hypertension-related diseases: a mixed-methods study. International Journal of Hypertension, (3), 1 – 9.
- [13] M'Buyamba-Kabangu, J.R., Anisiuba, B.C., Ndiaye, M.B., et al. (2013). Efficacy of newer versus older antihypertensive drugs in black patients living in sub-Saharan Africa. J Hum Hypertens, 27, 729–735.
- [14] Mills, K.T., Bundy, J.D., Kelly, T.N., Reed, J.E., Patricia M. Kearney, Reynolds, K., Chen, J., & He, J. (2016). Global disparities of hypertension prevalence and control a systematic analysis of population-based studies from 90 countries. Circulation, 134, 441–450. DOI: 10.1161/CIRCULATIONAHA.115.018912.
- [15] Okwuonu, C.G., Ojimadu, N.E., Okaka, E.I., & Akemokwe, F.M. (2014). Patient-related barriers to hypertension control in a Nigerian population. International Journal of General Medicine, 7, 345–353.
- [16] Oyebode, O., Oti, S., Chen, Y.F., & Lilford, R.J. (2016). Salt intakes in sub-Saharan Africa: a systematic review and meta-regression. Popul Health Metr, 14, 1.

- [17] Poornima, P., Raju, S., V. et al. (2014). "Factors influencing alcohol and tobacco addiction among patients attending a de-addiction Centre, South India." J Int Soc Prev Community Dent, 4 (2), 103-7.
- [18] Renu, T., Meenal, & Satwanti K. (2015). "Bio-Social Predictors of Hypertension among Premenopausal and Postmenopausal Women." SAGE open, 1-12.
- [19] Santschi, V., Chiolero, A., Colosimo, A.L., Platt, R.W., Taffé, P., Burnier, M., et al. (2014). Improving blood pressure control through pharmacist interventions: a metaanalysis of randomized controlled trials. Journal of American Heart Association, 3, (2), e000718.
- [20] U.S. Centers for Diseases Control. (2016). Medication adherence: action steps for health plan managers [online].
- [21] Ware, J.E., Kosinski, M., Bayliss, M.S., McHorney, C.A., Rogers, W.H., & Raczek, A. (1995). Comparison of

methods for scoring and statistical analysis of SF-36 health profiles and summary measures: summary of results from the Medical Outcomes Study. Medical Care, 33 (Suppl 4): AS264-AS279.

- [22] World Health Organization (2016). (Available from: http://www.who.int/nmh/ncd-tools/definition-targets/en/.) [13 Mar 2018]
- [23] World Health Organization (2015). Raised blood pressure: Situations and trends [Internet]. (Available from: http://www.who.int/gho/ncd/risk factors/blood pressure

http://www.who.int/gho/ncd/risk\_factors/blood\_pressure\_ prevalence\_text/en/) [20 Feb 2017].

[24] World Health Organization (2014). Global Status Report on Non Communicable Diseases [Internet]; 2014. (Available from: http://apps.who.int/iris/bitstream/10665/ 148114/1/9789241564854\_eng.pdf? ua=1)

