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RESEARCH ARTICLE

THE IMPACT OF DRUG COST ON MEDICATION ADHERENCE IN NIGERIA: A PERCEPTION AMONG PHARMACISTS

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Abstract

Background: Given Nigeria's huge economic instability, medication expenses may significantly impact medication adherence, creating a barrier to the treatment of various ailments. The study aimed to assess pharmacists' perceptions about the impact of drug costs on medication adherence in Nigeria.
Methods: The study was cross-sectional among practicing pharmacists across Nigeria. The 25 items semi-structured questionnaire was administered online using simple random sampling with the snowballing technique to recruit the pharmacists for the study. The collected data was coded into Microsoft Excel 2016 and subsequently analyzed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were utilized to summarize the data, providing an overview of the demographic characteristics and key findings. Inferential statistics, specifically Pearson's Chi-square test, were employed where applicable to determine the relationships between variables.
Results: Total 161 pharmacists responded to the survey, giving an 80.5% response rate. The respondent rate was mainly young pharmacists (20–30 years old; 82.6%) and predominantly male (51.6%). Almost all the respondents possess only a bachelor of pharmacy degree (91.9%). Total 90% have practiced for 5 years or less, mostly in community settings (60.9%). Generic substitution has been cited as the most important technique to manage drug costs. Non-adherence due to cost was associated with practice settings, whereas adherence counseling was correlated with gender and setting of practice. All differences were not statistically significant at $p<0.05$.
Conclusions: Most participants believe that the cost of medication is a major barrier to accessing quality healthcare and drives massive non-adherence among those who can barely afford the medicines. Implementing a comprehensive national strategy to enhance the healthcare system, expand the reach of the national health insurance program, and promote cooperation among healthcare practitioners will result in improved clinical outcomes for patients.
Keywords: Drug cost, medication adherence, Nigeria, pharmacists.

INTRODUCTION

Across the globe, healthcare systems are confronted with a variety of challenges, among which one of the most pressing is the need to ensure that patients consistently adhere to their prescribed medication regimens. Adherence to prescribed medications is fundamental to effective disease management and maintaining public health, yet it is influenced by a multitude of factors, among which the cost of drugs stands out as one of the most critical determinants, often impacting treatment plans. The affordability of drugs is crucial, as it can impact medication adherence, creating a financial barrier to effectively treating

diseases and managing conditions[1,2]. Elevated medication costs can also lead to poorer patient outcomes and unwarranted hospitalizations, particularly among those with low incomes. The expenses related to medication and tests impose a significant financial burden on patients, accounting for more than 88% of the total treatment cost[3]. Medication adherence plays a vital role in the healthcare system, as it has a direct impact on patient outcomes, overall quality of life, and the financial burden of healthcare. But a prominent challenge to achieving this is the steep cost of medications, a factor that is especially pronounced in low- and middle-income countries such as Nigeria, where financial constraints significantly hinder patients' ability to consistently follow prescribed treatment regimens[4,5]. The high cost of medications is a well-known obstacle to medication adherence, and in Nigeria, these elevated drug prices often compel patients to choose between healthcare and other essential living expenses[6]. In Nigeria, the high cost of medications is driven by multiple factors such as importation expenses, taxes, and limited local manufacturing capabilities, which often result in essential drugs being unaffordable for many, especially for those in lower-income brackets; this issue is aggravated by the lack of price regulation in the pharmaceutical sector, causing considerable price disparities across various regions and pharmacies[7]. Medication non-adherence poses a major challenge in public health, with research indicating that as many as half of all patients may not follow their prescribed treatment regimens, leading to widespread concerns about the effectiveness of medical interventions[4]. In Nigeria, the issue of medication non-adherence is further intensified by several other factors, including restricted access to healthcare services, a lack of comprehensive health insurance coverage, socio-economic status, cultural beliefs, and healthcare infra-structure, all of which contribute to the challenge of ensuring that patients follow their prescribed treatment regimens. Despite the essential role pharmacists play in healthcare, they often encounter a range of unique challenges, such as navigating the high cost of medications, dealing with frequent stock shortages, and addressing the financial constraints that many patients face, which can significantly impact their ability to afford necessary treatments[7]. Pharmacists roles are multifaceted in the healthcare system, and they are considered the most accessible healthcare team members among healthcare practitioners[8]. In addition to the long-standing roles of dispensing medications, patient education on healthy lifestyle changes, and medication use evaluation, the roles of pharmacists have extended to ensuring a significant level of adherence to the regimen of the prescribed medications as they interact directly with patients[9]. The ability of citizens to access and afford essential healthcare services is an important index for measuring the level of development of a nation[10]. Healthcare services are critical, especially in Nigeria, with a diverse population characterized by high birth rates and rapid aging among adults. Inaccessibility of healthcare always stems first from availability, then cost of the services, especially medications, and/or the presence of manpower to deliver the services. The high cost of medication and other healthcare services has major implications for non-adherence, even among the population that can manage to afford those[11]. In less developed nations like Nigeria, healthcare professionals must optimize patient resources to maximize health benefits. This study was therefore set up to investigate the perception of pharmacists on the cost of medicines in Nigeria and its impact on adherence levels among the patients.

METHODS

Study Design

This study adopted a descriptive cross-sectional survey design to explore pharmacists' perceptions of the impact of increased drug costs on medication adherence in Nigeria. Data was collected through structured questionnaires distributed virtually to licensed pharmacists across various regions of Nigeria.

Study Population

This study targeted licensed pharmacists working in community pharmacies, hospital pharmacies, and many other areas of pharmacy practice in Nigeria.

Sample Size

A sample size of at least 150 pharmacists was targeted to ensure adequate representation and reliable results. It was calculated using the Raosoft® Sample Size Calculator, assuming a 5% margin of error, a 95% confidence level, and a 50% response distribution. A purposive sampling method was used to select participants, as it allows for the selection of individuals who have the specific knowledge and experience required to address the research questions.

Data collection instrument and procedure

A semi-structured 25 items questionnaire was developed specifically for this study, comprising both closed-ended and open-ended questions to gather comprehensive data on pharmacists' perceptions. The questionnaire was divided into seven sections: demographic information, professional practice details, perception of drug costs, impact of drug costs on patient adherence, role of pharmacists in supporting adherence, open-ended questions, and additional comments.

The questionnaire was pre-tested in a pilot study with 20 pharmacists to ensure clarity, relevance, and reliability. Pharmacists were recruited through professional associations, online forums, and social media platforms, with invitations sent via email and social media messages, including a link to the online questionnaire hosted on platforms such as Google Forms or Survey Monkey. Before accessing the questionnaire, participants were provided with an informed consent form detailing the study's purpose, procedures, potential risks and benefits, confidentiality, and their right to withdraw at any time. Consent was obtained electronically.

Duration of Study

Data collection for this study was done from February to April 2024 to give the participant the maximum time to fill the questionnaire.

Data Analysis

The collected data was coded into Microsoft Excel 2016 and subsequently analyzed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were utilized to summarize the data, providing an overview of the demographic characteristics and key findings. These include frequencies, percentages, means, and standard deviations for the quantitative data. For the qualitative data from open-ended questions, thematic analysis was conducted to identify common themes and insights. Inferential statistics, specifically Pearson's Chi-square test, were employed where applicable to determine the relationships between variables. Logistic regression analysis was also used to identify factors associated with medication adherence. Statistical significance was set at $p<0.05$.

Ethical Considerations

The study did not involve human trials or the use of human subjects; thus, an exception was sought and obtained from the Health Research and Ethics Committee of the University of Nigeria Teaching Hospital (Reference Number: NHREC/05/01/2008B-FWA00002458-1RB00002323). Informed consent was sent electronically to all participants, detailing the study's purpose, procedures, potential risks and benefits, and their role in the study. Participants were assured that their participation is entirely voluntary and that they can withdraw from the study at any time without facing any consequences. To maintain participant confidentiality, all responses were anonymized, and data was securely stored and accessible only to authorized research team members. These measures were designed to protect the personal information of participants and ensure their privacy throughout the study, thereby upholding the highest ethical standards in conducting responsible and respectful research.

RESULTS

Only 161 of the 200 pharmacists working in Nigeria's six regions responded to the survey, yielding an 80.5% response rate. Table 1 displays the sociodemographic characteristics of the study population. 82.6% of the pharmacists are young, aged between 20 and 30 years, while there was a near equal representation of the male (51.6%) and female (48.6%) genders. Almost all the pharmacists possess just the Bachelor of Pharmacy degree (91.9%), while a paltry number achieved higher degrees. Pharmacists who have practiced for 5 years or less constitute more than 90% of the respondents. More than half of the pharmacists (60.9%) practice in a community setting. Total 31.7% of them are in hospital practice, while the rest (7.5%) are in many other areas of practice. Western Nigeria (55.9%) has the highest number of pharmacists practicing and participating in the study. All other regions had equal participation.

Table 1: Sociodemographic representation of the study participants (n=161).

S. N.	Variable	Frequency (%)
1.	**Age (yrs.)**	
	20-30	82.6
	31-40	16.8
	41-50	0.6
2.	**Gender**	
	Male	51.6
	Female	48.4
3.	**Educational qualification**	
	B. Pharm	91.9
	M. Pharm	4.3
	D. Pharm	3.1
	Others	0.6
4.	**Years of professional experience (yrs.)**	
	1-5	91.3
	6-10	6.8
	11-15	0.6
	16-20	0.6
	Greater than 20	0.6
5.	**Nature of pharmacy practice**	
	Community	60.9
	Hospital	31.7
	Others	7.5
6.	**Region of pharmacy practice**	
	Northern Nigeria	14.9
	Southern Nigeria	14.9
	Eastern Nigeria	14.3
	Western Nigeria	55.9

B. Pharm = Bachelor of Pharmacy; M. Pharm = Masters in Pharmacy; D. Pharm = Doctor of Pharmacy

Table 2 summarizes the key perception indices that pharmacists use to evaluate the level of medication adherence and cost in this study. A little above 50% of the pharmacists see less than 40 patients in a day, constituting mainly mixed populations of adults, children, and the elderly. It seems like the cost of medication is high, as 52.2% of the respondents reported a high cost of medications, while another

35.4% reported it to be high. The pharmacists admitted that patients often (31.7%) and sometimes (53.4%) struggle to pay for their medications. The cost of medication as a barrier to adherence was always reported (31.7%), often (41.0%), and sometimes (23.0%) to the pharmacists.

Most patients are non-adherent, as more pharmacists reported non-adherence among 20 or more of their patients. Pharmacists discussing medication costs with patients are a normal practice. 31.7% of pharmacists reported that they always discuss medication costs with their patients, while 35.4% reported that they do so frequently. Most of the pharmacists reported that their intervention in improving medication adherence was effective (61.5%), while another 32.3% were not sure if it improved it or not. Counseling patients on medication adherence was always (63.4%), often (24.0%), and sometimes (12.4%) by the pharmacists.

Table 2: Key perception indices of pharmacists on cost of medication and adherence level (n=161).

S. N.	Variable	Frequency (%)
1.	**Average number of patients served daily**	
	1-20	23.0
	21-40	36.6
	41-60	12.4
	61-80	12.4
	81 and Above	15.5
2.	**Primary patients demographics**	
	Children	0.6
	Adults	28.0
	Elderly	1.2
	Mixed	70.2
3.	**Cost of prescription medications in Nigeria**	
	Very Low	1.9
	Low	0.6
	Moderate	9.9
	High	52.2
	Very High	35.4
4.	**How often patients struggle to afford their medications**	
	Often	31.7
	Sometimes	53.4
	Rarely	14.3
	Never	0.6
5.	**How often patients report cost of medication as barrier to adherence**	
	Never	0.6
	Rarely	3.7
	Sometimes	23.0
	Often	41.0
	Always	31.7
6.	**Number of patients who are non-adherent due to high drug costs**	
	0-10	11.8
	11-20	13.0
	21-30	21.7
	31-40	18.6
	41-50	19.3
	> 50	15.5
7.	**How often pharmacists discuss medication costs with patients**	
	Never	0.6
	Rarely	4.3
	Sometimes	28.0
	Often	35.4
	Always	31.7
8.	**Effectiveness of pharmacist intervention in improving medication adherence**	
	Ineffective	1.9
	Neutral	32.3
	Effective	61.5
	Very Effective	4.3
9.	**How often pharmacists counsel patients on medication adherence**	
	Always	63.4
	Often	23.0
	Sometimes	12.4
	Rarely	0.6
	Never	0.6

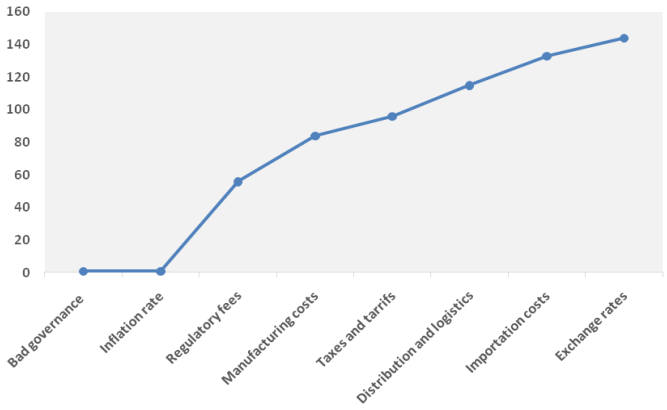

Figure 1: Representation of the factors contributing to high cost of medication in Nigeria.

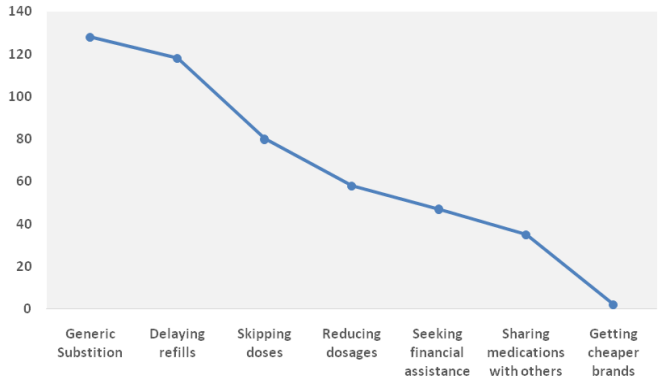

Figure 2: Various ways patients cope with high medication costs.

Figure 1 is a graphic representation of the various factors leading to High cost of medication in Nigeria. Exchange rates and importation costs led the way followed by distribution/logistics and manufacturing costs. Regulatory fees, inflation rate and bad government were least mentioned as one of the costs.

Figure 2 depicts the various ways patients cope with high medication costs. Most of the patients resort to generic substitutions or delay their refills in order to manage the limited resources. A few others reduce or entirely skip their dose as a way to cope with the high medication.

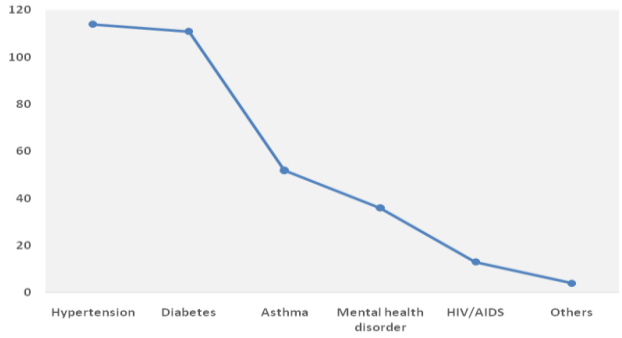

Figure 3: Chronic conditions with significant effect of drug cost on medication adherence.

Figure 3 illustrates the major chronic health conditions that significantly impact drug costs and medication adherence. More than 60% of the respondents mentioned diabetes and hypertension. They also mention mental health disorders and asthma, albeit to a lesser extent. HIV was the least common in this category. Figure 4 lists many techniques that pharmacists employ to aid patients in coping with high medication costs. Offering generic alternatives, education on the importance of adherence, and counseling on the proper use of medication were the most frequently employed. Providing access to financial aid and multi-disciplinary collaborations were the least used. Table 3 examined the association between the prevalence of non-adherence and the specialty and region of pharmacy practice. Community pharmacies consistently ranked higher in non-adherence for groups of patients. Compared to Northern and Eastern Nigeria, Southern and Western Nigeria had the highest prevalence of non-adherence. All differences were non-significant at *p* values less than 0.05. Table 4 shows the relationship between how often pharmacists discuss medication costs with patients and their gender, including their area of pharmacy practice.

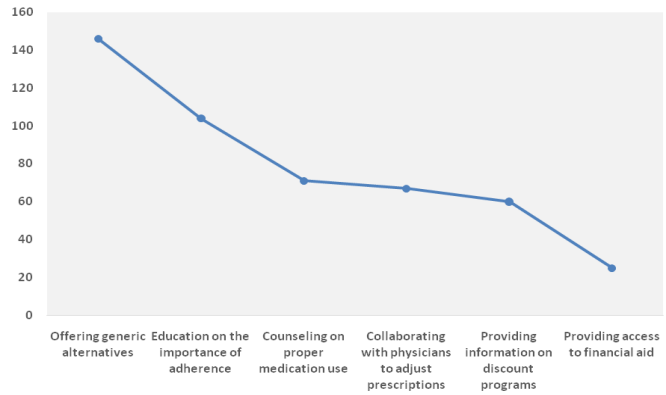

Figure 4: Strategies employed by pharmacists to help patients manage high medication costs.

Table 3: Chi Square level association between prevalence of non-adherence and the specialty and region of pharmacy practice.

S. N.	Variable	Number of non-adherent patients due to high cost of medications N (%)						*p* value
		0-10	11-20	21-30	31-40	41-50	>50	
1	**Specialty of Pharmacy Practice**							0.499*
	Community Pharmacy	13(13.3)	13(13.3)	20(20.4)	22(22.4)	19(19.4)	11 (11.2)	
	Hospital Pharmacy	4 (7.8)	7 (13.7)	11(21.6)	7 (13.7)	9 (17.6)	13 (25.5)	
	Others	2 (16.7)	1 (8.3)	4 (33.3)	1 (8.3)	3 (25.0)	1 (8.3)	
2	**Region of Pharmacy Practice**							0.892*
	Northern Nigeria	4 (16.7)	4 (16.7)	6 (25.0)	2 (8.3)	5 (20.8)	3 (12.5)	
	Southern Nigeria	4 (16.7)	1 (4.2)	5 (20.8)	4 (16.7)	6 (25.0)	4 (16.7)	
	Eastern Nigeria	3 (13.0)	1 (4.3)	5 (21.7)	6 (26.1)	4 (17.4)	4 (17.4)	
	Western Nigeria	8 (8.9)	15(16.7)	19(21.1)	18(20.0)	16(17.8)	14 (15.6)	

*Values are not significant at $p < 0.05$

Though insignificant, female pharmacists more often discuss medication costs with their patients compared to their male counterparts. Pharmacists in the community area of practice recorded more instances where they discussed the cost of medication with patients than those in hospital settings. These differences, however, were not statistically significant at $p<0.05$. Table 5 illustrates the impact of gender and the nature of pharmacy practice on the frequency of medication adherence counseling by pharmacists. More females (69.2%) always counsel their patients on medication adherence than males (57.8%). However, those in hospital practice focused more on patient counseling than pharmacists in community settings. All these differences, however, were not statistically significant at $p<0.05$.

Table 4: Association between how often pharmacists discuss medication costs with patients, gender and nature of pharmacy practice.

S.N.	Variable	How often pharmacists discuss medication costs with patients, N (%)					*p*-value
		Never	Rarely	Sometimes	Often	Always	
1	**Gender**						0.660*
	Male	0 (0)	3 (3.6)	26 (23.2)	30 (29.4)	24 (26.3)	
	Female	1 (1.3)	4 (5.1)	19 (24.4)	27 (34.6)	27 (34.6)	
2	**Nature of Pharmacy Practice**						0.973*
	Community Pharmacy Practice	1 (1.0)	4 (4.1)	27 (27.6)	33 (33.7)	33 (33.7)	
	Hospital Pharmacy Practice	0 (0.0)	3 (5.9)	15 (29.4)	19 (37.3)	14 (27.5)	
	Others	0 (0.0)	0 (0.0)	3 (25.0)	5 (41.7)	4 (33.3)	

*Values are not significant at $p < 0.05$

DISCUSSION

This study investigated the perception of pharmacists from the six political zones in Nigeria, on the cost of medicines in Nigeria and its impact on adherence levels among the patients. The study revealed significant impact of medication costs on patients' adherence and how the pharmacists employ counseling and generic substitutions to mitigate them. Nigeria is the most populous country in sub-Saharan Africa, with more than 200 million people[12]. Situated in the tropics, it is beset with many diseases, including malaria, parasitic diseases, HIV, and a host of other chronic diseases. While malaria and other infectious diseases have a staggering burden, chronic diseases such as hypertension and diabetes mellitus are also on the rise in the population. Lower life expectancies in Nigeria compared to developed nations have also led to a rise in chronic diseases and multimorbidity, placing significant strain on the overstretched healthcare system[13].

Table 5: Association between how often pharmacists counsel patients on medication adherence, gender and nature of pharmacy practice.

S.N.	Variable	How often pharmacists counsel patients on medication adherence, N (%)					*p*-value
		Always	Often	Sometimes	Rarely	Never	
1	**Gender**						0.374*
	Male	48 (57.8)	20 (24.1)	13 (15.7)	1 (1.2)	1 (1.2)	
	Female	54 (69.2)	17 (21.8)	7 (9.0)	0 (0.0)	0 (0.0)	
2	**Nature of Pharmacy Practice**						0.720*
	Community Pharmacy Practice	61 (62.2)	25 (25.5)	11 (11.2)	0 (0.0)	1 (1.0)	
	Hospital Pharmacy Practice	34 (66.7)	10 (19.6)	6 (11.8)	1 (2.0)	0 (0.0)	
	Others	7 (58.3)	2 (16.7)	3 (25.0)	0 (0.0)	0 (0.0)	

*Values are not significant at $p < 0.05$

Chronic conditions such as diabetes and neoplasm (cancer) were identified as the leading causes of morbidity among the older population attending a university hospital in Nigeria[14]. This corroborates current findings, in which the pharmacist reports the highest complaints about the cost of drugs from patients with hypertension and other chronic diseases.

Many of these diseases affect a population with low purchasing power, sending them into an unending cycle of unmet medical needs and deteriorating health conditions. Medication costs are between 10 and 17 percent of the total healthcare costs in most developed countries. In Nigeria and many other developing countries, medication costs can reach up to 70% of healthcare costs, proving detrimental to average family income[15]. The government's public health expenditure barely surpasses 4% of the national budget, amounting to about $11.2 per capita. Private funding and spending on healthcare, however, are at a record $49.8 per capita[16]. Even though this is higher than the average in many neighboring West African countries, it is still far below the global minimum of $86[12]. In current study, patients more often than not struggle to afford basic medications for their health needs, leading to a high rate of non-adherence. As previously mentioned, Discharge Against Medical Advice (DAMA) strongly correlates with a lower socioeconomic class, younger age, and lack of health insurance. This suggests that cost is a major factor in people stopping their health-seeking behaviors[15]. Increased public spending on healthcare is necessary to enhance healthcare accessibility for those with low incomes and reduce the financial burden of severe healthcare expenses on households. In Nigeria, healthcare insurance is still in its infancy and lacks widespread coverage[17]. Nigeria's health challenges necessitate a comprehensive approach involving cost-effective policies and interventions with clear political benefits for implementation.

Patient care encompasses more than just diagnosing and prescribing medicines; it also involves ensuring that these medicines are affordable and that patients use them appropriately in terms of dosage and timing. The first factor in this series is affordability, as it plays a crucial role in determining whether patients will initiate therapy in the first place[18]. Pharmacoeconomics and broad pharmaceutical care are attempts to ensure optimum outcomes for patients in all pharmacotherapy initiatives. This includes humanistic, clinical, and economic outcomes[19]. Pharmacist-led interventions, particularly in the area of optimizing treatment for affordability and clinical outcomes, are critical to ensuring the patient's satisfaction. In this study, the majority of pharmacists reported frequently engaging with their patients on issues of cost and adherence to their medications.

Lack of adherence is the champion of many antibiotic resistances and also portends treatment failure and complications among patients with chronic diseases[20]. Intervention by pharmacists, especially in the area of generic substitution, is important in combating the rising costs of medications in healthcare. Generics are chemical substitutes for branded drug products that possess the same dose, strength, and therapeutic efficacy. Pharmacists in this study offered generic substitutes as their number one strategy for improving adherence among their patients. This shows a high level of acceptance of generic substitutes by pharmacists as worthy alternatives to branded medicines. Community pharmacists in Nigeria exhibit a positive disposition towards the concept of generic medicines and their substitution, despite their continued preference for branded medicines[21]. Pharmacists in China reported wide acceptance of generic substitutes, but concerns about quality and efficacy persist[22]. A survey in Saudi Arabia and Ethiopia reported lower knowledge among pharmacists[23,24]. However, doctors do not always favour generics, citing lack of efficacy and therapeutic failures as key issues. In a study by Fadare *et al.*, doctors had poor knowledge of the cost of generics and brands of drugs, regardless of their role in pharmacoeconomic in drug prescribing[15]. This underscores the significant pressure doctors face when prescribing, often leading to complete neglect. Pharmacists who are well-trained in pharmacogenomics and optimizing patients' outcomes regardless of income are essential tools in bridging this gap.

This study also highlighted key differences in the operation of community pharmacies and hospital pharmacies, specifically in terms of patients' perceptions of costs and the pharmacists' efforts in counseling to encourage adherence. Obtained results showed that pharmacists in the hospital setting engaged more in medication counseling on adherence than their community pharmacists' counterparts. The trend reversed in the area of discussing the costs of

medicines with patients, as community pharmacists were more engaged than hospital pharmacists. This observation reflects a health behavioral model in healthcare delivery in Nigeria[25]. Patients have a higher level of trust in the doctors' prescriptions and are more willing to pay directly, which leads to less stress about the cost of medications[26]. The severity of diseases treated in the hospital setting compared to the community pharmacies, as well as the various specialties involved, contribute to this high level of confidence among patients. In a community setting, the pharmacist recommends over-the-counter (OTC) drugs and has to convince the patient because he or she needs them. Additionally, most patients in the community pharmacy are in a hurry. They just want to pick their medications and care less about counseling about adherence and drug use. Most other times, community pharmacists are more likely to push for branded medicines as opposed to generics in a bid to drive up profit. These key differences were highlighted by Atkinson *et al*., as he described that community pharmacists in most cases have to act as entrepreneurs while hospital pharmacists act within budget[27].

CONCLUSIONS AND RECOMMENDATIONS

This study reported significant effects on adherence by high medication costs among patients. Techniques such as patient engagement, generic and class substitution and patient counseling were employed by pharmacists both in the hospital and community settings to ameliorate these. Policies on advancing generics over branded drugs could help mitigate drug costs and thus improve adherence. Cost of medication is a major barrier to access to quality healthcare and also drives massive non-adherence among those who can barely afford the medicines. Pharmacists, by virtue of their training and set of skills are equipped to ensure affordability of medicines through generic substitution. They are also tasked to advocate adherence to medications especially antibiotics and drugs for chronic diseases through robust patient counseling and follow-up. Overall, a national policy to strengthen the healthcare system, increase coverage of the national health insurance scheme and ensure collaboration among healthcare professionals will lead to more positive clinical outcomes for patients.

Limitations of the study

The lack of statistical significance in this study might not be due to its absence but small sample size. Also, this study used a self-reported questionnaire in the data collection which might have influenced respondent's bias.

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AUTHOR'S CONTRIBUTION

Victor CA: Literature review, Data collation. **Evaristus JU**: conceptualization, data curation and drafting of the manuscript for this work. **Onyeka MA**: Methodology writing. **Fadilulahi AU:** Background of study, Data collection. **CJN, CUU, CSI, DMO, JOO, and DO:** Data collection, review. All authors reviewed the article and approved the final version.

DATA AVAILABILITY

Data will be available on request to anyone from the correspondence author.

CONFLICT OF INTERESTS

The authors declared no conflict of interests

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