

Drug therapy problem in elderly outpatients with benign prostatic hyperplasia

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ABSTRACT

Background: Benign Prostatic Hyperplasia (BPH) is a common non-malignant urological condition in ageing male. This disease is usually managed by medication and as a result, patients with BPH are exposed to Drug Therapy Problems (DTPs).

Objective: This study aimed to evaluate the prevalence and types of DTPs among elderly male with BPH in Nigeria.

Methods: A 10-year retrospective cross-sectional study was carried out among consecutively sampled elderly outpatients aged > 60 years with BPH at the Urology clinic of the Olabisi Onabanjo University Teaching Hospital, Southwest, Nigeria. The Pharmaceutical Care Network Europe Classification was used to classify DTPs. The six primary domains of Problem including adverse reactions, drug choice problem, drug use problem, interactions were explored. Drug-drug interactions (DDIs) were assessed using the Medscape® drug interaction checkers software. Chi-squared test or Fisher's exact as appropriate was used to determine associations between the domains and patients' clinical characteristics.

Results: A total of 201 medical records of participants, mean age 69.42 ± 7.36 years (R=60-91years) were evaluated, 35.8% had primary education and 29.9% had hypertension as comorbidity. Of the 120 DTPs (Mean \pm SD; 0.6 ± 0.2) identified among the participants, 55.8% involved DDIs, 16.7% drug choice problem and 15.0% drug use problem. Almost one-third of the DDIs (19/67; 28.4%) involved BPH medications. Co-morbidity was significantly associated with DDIs ($p < 0.001$), drug choice problem ($p < 0.001$) and drug use problem ($p < 0.001$).

Conclusion: Drug therapy problems are rife among elderly patients with BPH. Drug interactions and drug choice problems, including medication non-adherence are more prevalent than other types of DTPs.

Keywords: Drug therapy problem, Benign Prostatic Hyperplasia, Nigeria, Elderly, Drug use

Problèmes reliés à la pharmacothérapie chez les patients âgés ambulatoires atteints d'hyperplasie bénigne de la prostate dans un centre hospitalier universitaire nigérian

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RESUME

Contexte : L'hyperplasie bénigne de la prostate (HBP) est une affection urologique non maligne courante chez l'homme vieillissant. Cette maladie est généralement gérée par des médicaments et, par conséquent, les patients atteints d'HBP sont exposés à des problèmes reliés à la pharmacothérapie (PRP).

Objectif : Cette étude a été conçue pour évaluer la prévalence et les types de PRP chez les hommes âgés atteints d'HBP au Nigéria.

Méthodes : Une étude transversale rétrospective de 10 ans a été réalisée auprès de patients externes âgés de ≥ 60 ans atteints du HPB échantillonnés de manière consécutive à la clinique d'urologie du centre hospitalier universitaire Olabisi Onabanjo, dans le sud-ouest du Nigéria. La classification du Pharmaceutical Care Network Europe a été utilisée pour classer les PRP. Les six domaines principaux du problème comprenant des réactions indésirables, le problème du choix de médicaments, le problème de consommation de drogue, les interactions ont été explorés. Les interactions médicamenteuses ont été évaluées à l'aide du logiciel Medscape® Drug Interaction Checkers. Le test du chi carré ou le test exact de Fisher, le cas échéant, ont été utilisés pour déterminer les associations entre les domaines et les caractéristiques cliniques des patients.

Résultats : Un total de 201 dossiers médicaux de participants, d'âge moyen $69,42 \pm 7,36$ ans ($R=60-91$ ans) ont été évalués, 35,8% avaient une éducation primaire et 29,9% souffraient d'hypertension comme comorbidité. Sur les 120 PRP (moyenne \pm ET; $0,6 \pm 0,2$) identifiés parmi les participants, 55,8% concernaient des interactions médicamenteuses, 16,7% un problème de choix de drogue et 15,0% un problème de consommation de drogue. Près d'un tiers des interactions médicamenteuses (19/67; 28,4%) impliquaient des médicaments contre l'HBP. La comorbidité était significativement associée aux interactions médicamenteuses ($p < 0,001$), au problème de choix des médicaments ($p < 0,001$) et au problème de consommation de drogues ($p < 0,001$).

Conclusion : Les problèmes reliés à la pharmacothérapie sont monnaie courante chez les patients âgés atteints d'HBP. Les interactions médicamenteuses et les problèmes de choix des médicaments, y compris la non-observance des médicaments, sont plus fréquents que les autres types de PRP.

Mots-clés : Problème reliés à la pharmacothérapie, hyperplasie bénigne de la prostate, Nigéria, personnes âgées, usage de médicaments

INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a common urological disorder associated with ageing male with the global average between 26.2% and 28.8% among men aged 60 years and rising to about 50% in the eighth decade of life.^{1,2} Although, not life-threatening, BPH impacts negatively on patients' quality of life, increases healthcare costs and if untreated may result in complications such as renal insufficiency and bladder stone requiring surgical interventions.³ In Nigeria, more than 40% of elderly men above 90 years are affected.⁴

Medications remain the mainstay in the management of BPH, although a period of watchful waiting in which no medication is used is advocated in mild to moderate conditions.⁵ Several medications including the alpha-adrenergic blockers, 5-alpha-reductase inhibitors are standard recommendations in BPH. They may be used as monotherapy or in combination with other medications.⁶ Surgical interventions such as Transurethral Resection of the Prostate (TURP) are considered as a last resort as the disease deteriorates.⁷ Drug Therapy Problems (DTPs) including inappropriate prescribing, adverse drug reactions, drug interaction, drug choice problems and medication non-adherence have, however, been reported among elderly persons.⁸

Drug Therapy Problem is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes".⁹ Studies have estimated that approximately 10% of hospital admissions and about 30% of unplanned hospital visitation are due to DTPs.¹⁰ Adverse Drug Reactions (ADRs) occurs in about 10% of elderly during ambulatory or in-patient care and presents a huge cost to the healthcare system, while non-adherence to medication, apart from leading to poor clinical outcomes also contribute to increased healthcare utilization.^{11,12} The presence of comorbidity in the elderly predisposes them to polypharmacy leading to increased risk of drug-drug interactions.¹³

The Pharmaceutical Care Network Europe (PCNE) classifies DTPs into six primary domains for Problems, six primary domains for Causes and five primary domains for Interventions.^{11,14} The domain for Problem has six subtypes, coded P.1-6 including adverse reactions, drug choice problem, dosing problem, drug use problem, interactions and others respectively. This classification is validated and has been adapted for use in research and to assist healthcare professionals to document DTPs in the process of pharmaceutical care.¹⁵⁻¹⁷

Many prescribing criteria including the American Geriatrics Society-Beers (AGS-Beers) Criteria consisting of medications that should be generally avoided in the elderly or used cautiously in specific conditions have been developed to improve the safety of medicine use in elderly.¹⁸ Several of the medications commonly used in the management of BPH including antimuscarinic anticholinergics and Alpha-1 receptor blockers were included in the criteria which necessitates a careful and diligent selection of appropriate medications in this disease condition.

In Nigeria, studies have investigated DTPs in chronic diseases including hypertension, diabetes and kidney diseases.^{19,20} However, there is a dearth of studies specifically targeting elderly people who are at a higher risk of the DTPs than the general population. This study aimed to evaluate the prevalence and types of DTPs among elderly patients with BPH.

METHODS

Study design and settings

This was a 10-year retrospective cross-sectional study of medication utilization among consecutively sampled elderly outpatients with BPH at the Urology clinic of the Olabisi Onabanjo University Teaching Hospital, Sagamu, Southwest, Nigeria. The hospital is 255 bedded, situated in an urban city and provides tertiary healthcare services for many elderly people in the southwestern region of the country.

Study population, inclusion and exclusion criteria

The study population consisted of elderly male outpatients aged >60 years who had a diagnosis of BPH and attended the Urology department of the hospital between 1 June 2009 and 31 May 2019. Eligible participants that did not receive medication, had incomplete medical and personal information in their charts, or their records were not accessible at the time of the study, or were assessed during the pilot stage of the study were excluded.

Sample size determination

The sample size was determined using Raosoft® online software (<http://www.raosoft.com>). A previous study among Nigerian men had estimated the prevalence of BPH to be 23.7%.⁴ The total population of BPH patients in the hospital register during the study period was 522. Using this population, 24.0% prevalence rate and a 5% margin of error at a 95% confidence interval, a minimum sample size of 183 was calculated. An additional 10%

attrition rate was included to yield a maximum size of 201.

Data collection technique and instrument

The medical records of eligible participants were retrieved from the record office after normal working hours. The records were consecutively selected until the sample size was achieved. A checklist designed by the principal researcher was used to extract the data. The checklist which had earlier been pre-tested among ten patients in the hospital captured information including the participants' socio-demographic, co-morbid medical conditions, BPH complications, current BPH medications, concurrent medication and AGS-Beers' potential inappropriate medications. Other treatment procedures apart from pharmacotherapy undergone for BPH by the participants were noted. This is considered necessary to evaluate any potential medication appropriateness in such procedure.

The medical charts were reviewed by a clinical pharmacist in academia with almost 20 years of experience. The PCNE Classification Version 5.01 was used as a tool to classify DTPs.⁹ The six primary domains of the Problem were explored. These include adverse reactions, drug choice problem, dosing problem, drug use problem, interactions and others which include patient's dissatisfaction with therapy and therapy failure of unknown origin.

Drug-drug interactions (DDIs) in the participants' prescriptions were assessed using the Medscape® drug interaction checkers software (www.medscape.com). Only drug interactions classified as "serious" or "monitor closely" and "contraindicated" were evaluated in this

study. The doses of medication were evaluated for correctness using the 2018 British National Formulary.²¹ The physicians' notes on adverse drug reactions, patient's adherence and complaints about their medications were relied on in this study.

The drug choice problem subdomain of the PCNE version 5.01 was evaluated using the 2015 AGS- Beers Criteria to determine the appropriateness of the medication prescribed.¹⁸ Only medications listed to be avoided in the 2015 AGS-Beers Criteria with 'strong strength of recommendation' were considered as DTPs in this study in line with a previous study.¹⁶ The data were collected between 3rd June and 30th September 2019.

Data management and statistical analyses

The data in the checklist were manually entered into Excel worksheet and cleaned. The clean data were analysed using the Statistical Packages for the Social Sciences version 20 (SPSS, IBM Corporation, Armonk, NY, USA). Data were primarily analysed using descriptive statistics including frequency and percentage. The patients' variables were cross-tabulated with the types of DTPs and Chi-squared test or Fisher's exact as appropriate was used to determine association between the variables. $P < 0.05$ was considered significant.

RESULTS

Socio-demographics of the participants

A total of 201 medical records of participants, mean age 69.42 ± 7.36 years (R=60-91years) were evaluated. The majority of the participants (167/201; 83.1%) had formal education and 86.6% were married. The details are as presented in Table 1.

Table 1: The sociodemographic of the participants

Variables	Frequency (n=201)	Percentage (%)
Age		
60-69	108	53.7
70-79	68	33.8
80-89	22	10.9
90-99	3	1.5
Ethnicity of the respondents		
Yoruba	176	87.6
Igbo	10	5.0
Hausa	3	1.5
Others	12	6.0
Educational qualification		
Primary	72	35.8
Secondary	43	21.4
Tertiary	52	25.9
No formal education	34	16.9
Marital status		
Single	27	13.4
Married	174	86.6

Clinical characteristics of the participants

Many participants, 36.3% (73/201) had comorbidities with 29.9% (60/201) having hypertension as comorbidity and 50.2% had other urological conditions including Bladder Outlet Obstruction (Table 2).

Table 2: Clinical characteristics of the evaluated participants

Variables	Frequency	Percentage (%)
Hypertension	60	29.9
Diabetes mellitus	18	8.9
Asthma	9	4.5
Nephritis	5	2.5
Hyperlipidemia	2	1.0
Chronic kidney disease	2	1.0
Others*	4	2.0
BPH associated urological conditions (n=101)		
Bladder Outlet Obstruction	45	22.4
Chronic Urinary Retention	3	1.5
Hematuria	5	2.5
Cancer of the Prostate	26	12.9
LUTS**	16	7.9
Prostatitis	4	2.0
Urethral injury	2	1.0

*include hernia, cataract, hepatomegaly, erectile dysfunction, secondary infertility

**LUTS=lower urinary tract symptoms

Classes of BPH medications commonly prescribed

Of the 201 prescriptions evaluated, alpha-blockers (66.7%) were the most commonly prescribed class of BPH medications and tamsulosin was prescribed to 51.2% (103/201) of the study participants (Figure 1).

Monotherapy was used in 74.1% (149/201) of cases, combination therapy 18.9% (38/201) while other treatment procedures including surgery accounted for remaining 7.0% (14/201). The individual medications are presented in supplement 1.

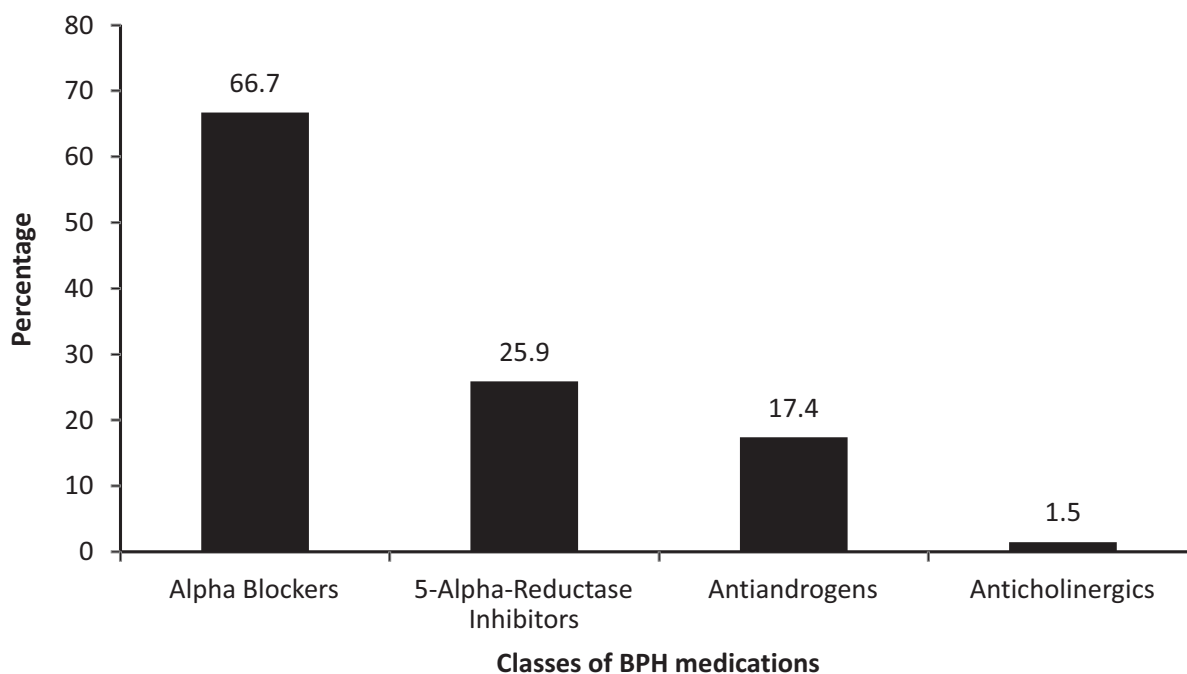


Figure 1: Classes of BPH medications used by patients

NB: A patient may receive more than one BPH medication

Supplement 1: BPH medication utilization among the participants

Variables	Frequency*	Percentage (%)
Tamsulosin	103	51.2
Alfuzosin	20	10
Doxazosin	10	5
Prazosin	1	.4
Terazosin	1	.4
Dutasteride	31	15.4
Finasteride	21	10.4
Bicalutamide	11	5.4
Flutamide	24	11.9
Tolterodine	2	1

* Note: The number may not add up to 201 because a patient may receive more than one BPH medication

Types of drug problems encountered

Antihypertensives 28.4% (57), diuretics 20.9% (42), analgesics 20.4% (41) and antibiotics 15.9% (32) were most frequently prescribed concurrently with BPH medication among the participants.

A total of 120 DTPs (Mean \pm SD; 0.6 \pm 0.2) were identified among the participants. Drug interaction was the most common type constituting 55.8% (67/120) of the DTPs (Table 3).

Table 3: Types of drug therapy problems encountered among the participants

Primary Domain	Frequency	Percentage
1. Adverse reactions		5.0
Side effects suffered (non-allergic)	6	
Side effects suffered (allergic)	0	
Toxic effects suffered	0	
2. Drug Choice Problem		16.7
Inappropriate drug	20	
Inappropriate drug form	0	
Inappropriate duplication of therapeutic group	0	
Contraindication for drug	0	
No clear indication for drug use	0	
No drug prescribed but clear indication	0	
3. Dosing Problem		5.8
Drug dose too low or dosage regimen not frequent enough	0	
Drug dose too high or dosage regimen too frequent	4	
Duration of treatment too short	3	
Duration of treatment too long	0	
4. Drug Use Problem		15.0
Drug not taken/administered at all (Adherence)	18	
Wrong drug taken	0	
5. Interactions		55.8
Potential drug interactions	67	
Manifest interactions	0	
6. Others		1.7
Patient's dissatisfaction with the drug despite taking the drug correctly	2	1.7
Therapy failure (reasons unknown)	0	
Total	120	

Drug interactions involving BPH medications

Of the potential drug interactions (67/120; 55.8%) identified, 28.4% (19/67) involved BPH medications.

Alfuzosin 13.4% (9/67) and tamsulosin 13.4% (9/67) were the most commonly implicated BPH medications in the interactions (Table 4).

Table 4: Drug-drug interactions involving BPH medications

Monitor closely	
BPH medication	Other medications
Tamsulosin	metronidazole+acetaminophen
Tamsulosin +bicalutamide	
Tamsulosin+ finasteride	ketoconazole+cefepodixime
Alfuzosin	diazepam+indapamide+ramipril
Alfuzosin	mist potcitrate+diclofenac
Alfuzosin	toremide+amlodipine+lisinopril+salmeterol
Alfuzosin	diazepam+lisinopril+toremide,metoprolol
Alfuzosin	metformin+amlodipine+losartan+insulin
Tamsulosin	doxycycline+ofloxacin+amlodipine+lisinopril
Tamsulosin	hyoscine+fluoxetine+olanzepine+ofloxacin+diclofenac
Alfuzosin+flutamide	diazepam+lisinopril,toremide+metoprolol+ephedrine
Biclutamide+alfuzosin	ofloxacin+metronidazole+diclofenac
Alfuzosin	ciprofloxacin+acetazolamide+doxycycline
Alfuzosin	carvedilol+losartan+spironolactone+furosemide+salmeterol
Tamsulosin	acetaminophen+amlodipine+lisinopril+hydrochlorthiazide+mistpot citrate
Tamsulosin	metronidazole+ofloxacin+diclofenac+mist pot citrate
Tamsulosin	ephedrine+theophylline+orphenadrine+acetaminophen
Serious drug interaction	
Doxazosin	amlodipine+atorvastatin+toremide+ramipril+losartan

Source: Medscape drug interaction checker

Patients' variables and drug therapy problem

Co-morbidity was significantly associated with DDIs ($p<0.001$), drug choice problem ($p<0.001$) and drug use problem ($p<0.001$) among the participants (Table 5).

Table 5: Association between patients' variables and the most prevalent types of DTP

Variables	Drug interaction			Drug choice problem			Drug use problem		
	Yes (%)	No (%)	P-value	Yes	No	P-value	Yes	No	P-value
Age									
60-69	46 (22.9)	62 (30.8)		15 (7.5)	93 (46.3)		16 (8.0)	92 (45.8)	
70-79	15 (7.5)	53 (26.4)	0.037*	4 (2.0)	64 (31.8)	0.201*	2 (1.0)	66 (32.8)	0.037*
80-89	6 (3.0)	16 (8.0)		1 (0.5)	21 (10.4)		0 (0.0)	22 (10.9)	
90-99	0 (0.0)	3 (1.5)		0 (0.0)	3 (1.5)		0 (0.0)	3 (1.5)	
Educational qualification									
Primary	21 (10.4)	51 (25.4)	0.441	3 (1.5)	69 (34.3)	0.022*	4 (2.0)	68 (33.8)	
Secondary	14 (7.0)	29 (14.4)		7 (3.5)	36 (17.9)		10 (5.0)	33 (16.4)	0.002*
Tertiary	22 (10.9)	30 (14.9)		9 (4.5)	43 (21.4)		0 (0.0)	52 (25.9)	
No formal education	10 (5.0)	24 (11.9)		1 (0.5)	33 (16.4)		4 (2.0)	30 (14.9)	
Comorbidities									
Yes	43 (21.4)	30 (14.9)	<0.001	18 (8.9)	55 (27.4)		17 (8.5)	56 (27.9)	<0.001*
No	24 (12.0)	104 (51.7)		2 (1.0)	126 (62.7)	<0.001*	1 (0.5)	127 (63.2)	
BPH associated Urological condition									
Yes	36 (17.9)	65 (32.3)	0.485	6 (3.0)	95 (47.3)	0.056	16 (8.0)	85 (42.3)	<0.001*
No	31 (15.4)	69 (34.3)		14 (7.0)	86 (42.8)		2 (1.0)	98 (48.7)	

*Fisher's Exact p-value

About 10.0% of the participants (20/201) were prescribed at least one PIM according to the 2015 AGS-Beers Criteria. Methyldopa (5/201; 2.5%) and diazepam

alone or in combination (5/201; 2.5%) were more frequently inappropriately prescribed medications to the participants.

DISCUSSION

Drug therapy problem is a major healthcare concern because of its association with morbidity and mortality, especially in the elderly population.²² In this study, 120 DTPs were identified in the prescriptions of the elderly patients, of which potential drug interactions (55.8%), followed by drug choice problem (16.7%) and drug use problem (15.0%) were the most common types. This finding contradicts a similar study among Malaysians with BPH that reported drug choice problems (45.9%) as being the most common DTPs.¹⁶ The variation in the finding of this study and the Malaysians' is probably a reflection of the differences in the study population, healthcare systems and the knowledge and alertness of the practitioners to DTPs in the settings.

The prevalence of potential drug interactions in this study is higher than reported in a similar study among Malaysians (24.9%) with BPH.¹⁶ It should be noted, however, that this present study unlike the Malaysian included specifically elderly patients. The elderly because of comorbidities tend to consume more medications and this predisposes them to more drug-drug interactions than their younger colleagues.²³ Similar studies that applied the same tool (PCNE) among Nigerians with kidney diseases and type 2 diabetes reported a lower prevalence of 36.7% in both disease conditions.^{19,20}

It is worthy of note that almost one-third of the drug interactions in this study involved BPH medications and at least three of the interactions (15.8%) are of clinical importance. The combinations of alfuzosin + carvedilol and alfuzosin + metoprolol require modification of therapy and indeed the combinations were responsible for the two serious cases of hypotension experienced by the study participants. A combination of tamsulosin and metronidazole required dose reduction for codeine and paracetamol (Cocodamol)[®] that were co-administered for a patient. Metronidazole increases the level of tamsulosin by inhibiting hepatic enzyme CYP3A4 metabolism. Therefore, a dose reduction is recommended for co-administered drugs such as codeine, paracetamol and diazepam that are predominantly metabolized by CYP3A.²⁴ This episode accounted for a case of dosing problem (dose too high) and adverse drug reactions (prolonged dizziness) among the study participants.

Inappropriate medication prescribing was the only drug choice problem encountered among the drug choice problems and accounted for 16.7% of the DTPs. This prevalence is lower than previously reported in a study

that applied these same criteria among the Malaysians.¹⁶ Methyldopa and diazepam were most involved in the inappropriate drug choice. Both drugs are listed as inappropriate by the AGS-Beers Criteria due to high risks of causing postural hypotension and fall respectively in elderly people.¹⁸ Prazosin, a non-selective alpha-adrenergic blocker is not advocated for use in BPH again due to its systemic adverse effects including hypotension and dizziness and it indeed actually caused postural hypotension in a patient that was prescribed the medication. Physicians need to be more aware of the AGS-Beers Criteria recommendations.

Medication non-adherence was the only form of drug use problem encountered in this study. The prevalence of MA in this study is comparable with previous Nigerian studies among elderly in-patients (14.4%) in the same hospital and (13.8%-15.4%) among patients with hypertension/diabetes in the Niger-Delta region.^{25,26} It is, however, lower than 29%-35% reported among Italians with BPH.⁵ The difference in the prevalence may be due to the differences in the study populations and the medications evaluated. Several reasons may account for this high non-adherence including the cost of BPH medication which may be unaffordable to older persons in Nigeria, majority of who spend out of pocket.³ Adverse effects of BPH medications may also be another factor. It is generally known that adherence to BPH medication is low (29%-35%) depending on the medication and whether a monotherapy or combination therapy is used.^{5,8} In this study, tamsulosin was most frequently used but it has been associated with a higher risk of dementia among elderly patients.²⁷ Generally, alpha-adrenergic blockers are associated with dizziness, postural hypotension and headache which may influence patient's adherence to the medication.²⁸

Co-morbidity is an associated factor for drug interactions, drug choice problem and drug use problem among the participants. This is understandable because comorbidity is associated with polypharmacy which can predispose to drug-drug interactions and promote patients' non-adherence to medications.²⁹ Besides, multiple guidelines used in the management of co-morbidities especially in the elderly, may present a challenge to physicians in the choice of appropriate medications and may complicate pharmacotherapy leading to patient's non-adherence.

This study is perhaps the first to evaluate DTPs among Nigerians with BPH and specifically among the elderly. It, however, has some limitations. The study being retrospective did not evaluate the actuality of the identified DTPs. The prevalence of DTPs might have been underestimated since some relevant clinical data and physicians' notes were not available in a few of the medical records. The study relied on patients' self-reported medication adherence as documented by the physicians and this could have resulted in an overestimation of the patients' adherence. Interventions by physicians and pharmacists and the outcome of the intervention as listed in PCNE were not evaluated in this study. The dearth of study on DTPs in BPH among Nigerians made it difficult to compare the findings of the present study with others. This study was carried out in a teaching hospital and may not, therefore, be generalisable to other healthcare facilities in Nigeria.

CONCLUSION

Drug therapy problems are frequently encountered among elderly patients with BPH. Drug interactions and drug choice problems are more prevalent than other types of drug therapy problems in this category of patients. It is therefore important that clinical tools for easy detection and assessment of these types of drug therapy problems are made available to prescribers and pharmacists to improve the quality of care to elderly patients with Benign Prostatic Hyperplasia. There is a need for improvement of pharmaceutical care to compliment the medical care being offered to elderly patients.

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