ORIGINAL RESEARCH ARTICLE

THE PREVALENCE OF 5 ALPHA REDUCTASE INHIBITOR ADVERSE EVENTS IN PATIENTS WITH BENIGN PROSTATIC HYPERPLASIA IN JAMAICA

Abstract

Aim: To determine the prevalence of adverse effects of 5-ARIs in patients with BPH in Jamaica.

Study Design: A Prospective Cohort Study

Place and Duration of Study: Genitourinary Outpatient Departments at the University Hospital of the West Indies and Kingston Public Hospital in Kingston, Jamaica between September 2021 and September 2022.

Methodology: We included 80 patients with inclusion criteria: all patients with symptomatic BPH being commenced on 5-ARIs with no prior history of conditions considered as adverse effects. Patients were administered a two-time descriptive questionnaire designed to assess the recognized adverse effects of 5-ARIs. The change from baseline to interval follow-up on the Male Sexual Health Questionnaire (MSHQ) erection, ejaculation, sexual desire scores and Hospital Anxiety and Depression Scale Depression subscale (HADS-D) score and the development of gynaecomastia (primary outcomes) and personal stressors experienced (secondary outcome) were assessed, using a standard software package.

Results: Ten percent of patients self-reported adverse effects. There was a statistically significant reduction (worsening) in the MSHQ erection score from baseline (34.08; sd 8.99) to 33.26 (sd 9.42; p=0.05) after commencing 5-ARI

but no significant change in ejaculation (difference of 0.43; p= 0.15) and sexual desire (difference of 0.01; p=0.98) scores. No signs of depression were noted in patients taking 5-ARI up to 6 months with the mean HADS-D score at baseline being 2.66 with no significant change at follow-up (2.50; p = 0.24). The development of gynaecomastia was not significant (p= 0.630). The proportion of patients who experienced personal stressors was lower after commencing 5-ARIs compared with baseline (8 patients; 10% vs 33 patients; 41.25%).
Conclusion: 5-ARIs are associated with a reduction in MSHQ erection score within 6 months of therapy and may correlate to the onset of erectile dysfunction.

Keywords

BPH, 5-alpha reductase inhibitor, post-finasteride syndrome, sexual dysfunction, erectile dysfunction, depression

Introduction

Benign prostatic hyperplasia (BPH) is a common condition experienced by men over 50 years of age, the prevalence of which increases with age [1]. The prevalence is approximately 50% in men in the 5th decade and 80% in men in the 8th decade of life. About 25% of men will be treated for BPH by the age of 80 [1]. Dihydrotestosterone (DHT), a testosterone derivative with a greater affinity for the androgen receptor, influences both normal prostate development and the progression of BPH [2]. The conversion of testosterone to DHT is carried out by the enzyme 5-alpha reductase. 5-alpha reductase inhibitors (5-ARIs) incite prostatic epithelial involution, slowing the progression of BPH by lowering serum and intraprostatic DHT concentrations [3]. Two 5-ARIs exist presently; finasteride and dutasteride.

Despite the benefits of these medications in the treatment of BPH, they are not without their adverse effects. Complications from 5-ARI use most frequently fall into the category of sexual side effects, affecting 3.4 to 15.8 percent of men [4]. Of these, the most prevalent side effect is erectile dysfunction followed by ejaculatory dysfunction, loss of libido and decreased ejaculatory volume [4].

5-ARIs have also been linked to psychiatric adverse events including depression, suicidal ideation and anxiety [5,6]. Additionally, there is an increased risk of gynaecomastia with 5-ARIs, with some studies demonstrating a 4.5% risk [7].

The constellation of all these adverse effects of 5-ARIs lead to the establishment of the term post-finasteride syndrome. Post-finasteride syndrome has now been included in the National Institute of Health's Genetic and Rare Diseases Information Center (GARD). Currently, no studies exist establishing the prevalence of these adverse effects in Jamaican men being treated with 5-ARIs for their BPH. Developing knowledge of this will aid in optimal patient counselling prior to the commencement of these medications by local urologists as well as facilitate screening for these adverse effects and managing accordingly to improve the quality of life in this patient population. The goal of this study was to determine the prevalence of adverse effects (sexual dysfunction, depression and gynaecomastia) of 5-ARIs in patients with BPH in Jamaica.

Methodology

Study design and Patient Entry Criteria

A prospective cohort study was conducted at the Genitourinary Outpatient Departments at the University Hospital of the West Indies and Kingston Public Hospital in Kingston, Jamaica between September 2021 and September 2022.

Ethical approval was granted from the Ethics Committee for the respective institutions.

The study population comprised of patients with BPH treated with 5-ARIs. All patients with a diagnosis of symptomatic BPH being commenced on 5-ARIs were identified by the urologist and directed to a research assistant who was independent of the medical team. Patients with a prior history of the conditions being classified as adverse effects (erectile dysfunction, ejaculatory dysfunction, reduced libido, depression, suicidal ideations and gynaecomastia) were excluded.

Eligible patients were invited to participate in the study and written informed consent was obtained from the participants.

Eligible patients were administered a two-time descriptive questionnaire survey designed to assess the adverse effects of 5-ARIs experienced. The survey encompassed items from the Male Sexual Health Questionnaire (MSHQ) and the Hospital Anxiety and Depression Scale Depression subscale (HADS-D) to qualify the effects, as well as questions evaluating demographics, social and medical characteristics including chronic illnesses, smoking history and exercise routine. Additionally, inclusion was made for patient reported adverse effect. Initially, the questionnaire was interviewer-administered in private setting to ensure patient comfort and confidentiality and subsequently telephone-administered at an interval from 6 weeks to 6 months after commencing 5-ARIs. Patients who were not able to be followed up via telephone were censored.

Endpoints

Primary endpoints

The primary endpoints were the change in sexual function from baseline measured by change in MSHQ scores (higher scores indicate better sexual

function [8]) in domains: erection (questions 1–3; range 0–15), ejaculation (questions 5–11; range 1–35) and sexual desire (questions 19-25; range 1-35); change from baseline in HADS-D score (range 0-21; a score of ≥11 indicates a clinically significant disorder, while a score between 8 and 10 indicates a mild disorder [9]) and the development of gynaecomastia (subjective increase in breast size), at an interval from week 6 to month 6.

Secondary endpoints

The change from baseline in personal stressors experienced was assessed as a secondary endpoint at an interval from week 6 to month 6.

Statistical Analysis

All patients with data at baseline and at follow up interval from 6 weeks to 6 months were included in the analyses. The outcomes that were assessed were change in HADS-D score and scores for the MSHQ domains (erection, ejaculation and sexual desire) and the development of gynaecomastia (primary outcome) and personal stressors experienced (secondary outcome). Self-reported adverse effects were also assessed. The variables: MSHQ erection, ejaculation, sexual desire scores, HADS-D score, gynaecomastia and personal stressors were assessed.

Data were expressed as frequencies and means with standard deviations. Change in HADS-D score and scores for the MSHQ domains (erection, ejaculation and sexual desire) were measured based on change in scores from baseline to interval follow-up from 6 weeks to 6 months. Differences were assessed by paired t-test. Change in scores by type of 5-ARI (dutasteride vs finasteride) was assessed by mixed regression analysis. Incidence of gynaecomastia was expressed as a proportion and analysed by binomial test. Change in personal stressors were expressed as frequencies and percentages.

The self-reported adverse effects were conveyed by frequencies. All statistical analyses were performed using a standard software package (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). All P values reported were two-sided with $P \leq 0.05$ considered statistically significant.

Results

Study Population

94 patients were recruited. However, 14 patients were lost to follow-up and a total of 80 participants were finally included in the study. The mean age (sd) of the participants was 65.8 (7.5) years. Baseline demographics, social, and medical characteristics of the participants are shown in Table 1.

Results of Patient- Reported Adverse Effects

Of the 80 patients included in the study, 8 (10%) self-reported adverse effects related to 5-ARI. Erectile dysfunction was reported by 2 patients. In one patient this adverse effect was experienced after 3-6 months of commencing dutasteride and its severity remained the same with continued usage of the drug and it did not result in non-compliance while in the other patient this adverse effect was experienced within 1 month of dutasteride use with worsening severity with continued usage and it resulted in non-compliance. The other reported adverse effects included drowsiness, bloating, insomnia and constipation. Drowsiness was reported by 2 patients, the severity of which improved in one patient maintained on finasteride for more than 6 months and remained the same in one patient maintained on dutasteride for 3-6 months; the presence of this adverse effect had no impact on compliance in either patient. Bloating was reported by 2 patients maintained on dutasteride. The bloating improved in one patient who was on dutasteride for more than 6 months and remained the same in another patient maintained on the drug for 3-6 months. In neither was compliance

affected. Insomnia was reported by 1 patient within 1 month of commencing dutasteride; the presence of which affected compliance to the drug. Constipation was reported by 1 patient on dutasteride for 3-6 months; the constipation improved with time and did not affect compliance (Table 2).

Primary Endpoints

No signs of depression were noted in patients taking 5-ARI up to 6 months. The mean HADS-D score at baseline was 2.66 with no significant change in post-baseline score (2.50; p = 0.24; Table 4). For the erection domain, there was a statistically significant reduction (worsening) in the erection score from baseline (34.08; sd 8.99) to 33.26 (sd 9.42; p=0.05) after commencing 5-ARI (Table 4). This reduction in the erection score was independent of the type of 5-ARI used; with dutasteride the erection score was reduced from baseline (34.3; sd 9.1) to 33.6 (sd 9.6) and finasteride resulted in a reduction from 31.6 (sd 8.6) at baseline to 30.1 (sd 6.9) (Table 3). There was no significant change in ejaculation (difference of 0.43; p= 0.15) and sexual desire (difference of 0.01; p=0.98) scores from baseline to post treatment (Table 4). The development of gynaecomastia post treatment was not significant (p= 0.630; Figure 1).

Secondary Endpoint

The proportion of patients who experienced personal stressors was lower post treatment compared with baseline (8 patients; 10% vs 33 patients; 41.25%; Table 5).

Table 1. Baseline demographics and patient characteristics

Parameters	5-Alpha Reductase Inhibitor		
	Dutasteride	Finasteride	All (n=80)
Age, years			
Mean	65.5	68.9	65.8
sd	7.5	7.7	7.5

Chronic Illnesses, n (%)			0.294 (p value)
No	37 (46.25)	5 (6.25)	42 (52.50)
Yes	36 (45)	2 (2.50)	38 (47.50)
Hypertension, n (%)			0.397 (p value)
No	40 (50)	5 (6.25)	45 (56.25)
Yes	33 (41.25)	2 (2.50)	35 (43.75)
Diabetes, n (%)			0.883 (p value)
No	61 (76.25)	6 (7.50)	67 (83.75)
Yes	12 (15)	1 (1.25)	13 (16.25)
Smoking History, n (%)			0.992 (p value)
Non-smoker	32 (40)	3 (3.75)	35 (43.75)
Ever-Smoker	41 (51.25)	4 (5)	45 (56.25)
Regularity of Exercise, n (%)			0.162 (p value)
None	41 (51.25)	2 (2.50)	43 (53.75)
Regular Exercise	32 (40)	5 (6.25)	37 (46.25)

Table 2. Summary of reported adverse effects

Adverse Effect	Dutasteride	Finasteride	Duration for onset	Severity with continued usage	Effect on Compliance

Erectile Dysfunction					
	□		3-6 months	Same	No
	□		<1 month	Worsened	Yes
Drowsiness					
		□	>6 months	Improved	No
	□		3-6 months	Same	No
Bloating					
	□		>6 months	Improved	No
	□		3-6 months	Same	No
Insomnia	□		<1 month	Same	Yes
Constipation	□		3-6 months	Improved	No

Table 3. Change in HADS-D score and scores for the MSHQ domains (erection, ejaculation and sexual desire) from baseline to interval follow-up

	Dutasteride	Finasteride	All
HADS-D score baseline			
mean	2.7	2.6	2.7
sd	2.1	1.7	2.1
HADS-D score post			
mean	2.5	2.7	2.5
sd	2.3	1.8	2.2
Erection score baseline			
mean	34.3	31.6	34.1
sd	9.1	8.6	9.0
Erection score post			
mean	33.6	30.1	33.3
sd	9.6	6.9	9.4
Ejaculation score baseline			
mean	24.4	23.1	24.3
sd	6.9	5.8	6.8
Ejaculation score post			
mean	24.1	21.9	23.9
sd	7.7	4.6	7.5
Sexual desire score baseline			
mean	13.7	12.4	13.6
sd	3.3	3.1	3.3
Sexual desire score post			
mean	13.8	11.3	13.6
sd	5.0	1.8	4.9

Table 4. Summary of analysis for change from baseline in HADS-D score and scores for the MSHQ domains (erection, ejaculation and sexual desire)

	Baseline	Post 5-ARI Drug	Difference	*P* value
HADS-D Score				
mean	2.66	2.50	0.16	.24
sd	2.06	2.23		
Erection Score				
mean	34.08	33.26	0.81	.05
sd	8.99	9.42		
Ejaculation Score				
mean	24.29	23.86	0.43	.15
sd	6.78	7.46		
Sexual desire Score				
mean	13.59	13.58	0.01	.98
sd	3.28	4.85		

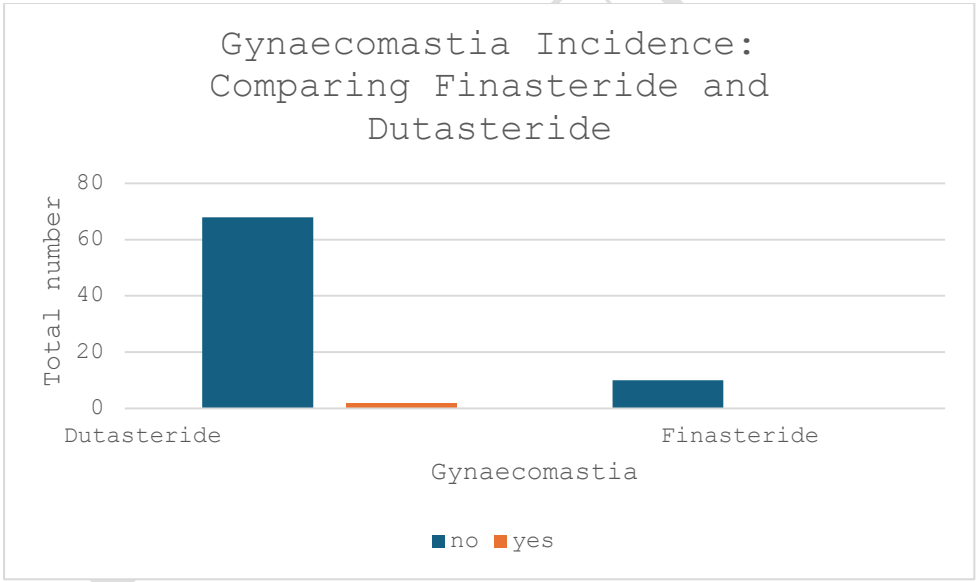

Figure 1. Bar chart showing gynaecomastia incidence: comparing finasteride and dutasteride

P value .63

Table 5. Change in personal stressors experienced from baseline to interval follow-up

	Post Personal Stressors, n (%)		Total, n (%)
Baseline Personal Stressors, n (%)	No	Yes	
No	47 (58.75)	0 (0)	47 (58.75)
Yes	25 (31.25)	8 (10)	33 (41.25)
Total	72 (90)	8 (10)	80 (100)

McNemar's chi2(1) = 25.00 Prob > chi2 = 0.0000

Discussion

This study is the first to prospectively assess adverse effects related to 5-ARIs in patients with BPH in Jamaica. The results from the study provide valuable insights into the safety profile of these medications for patients in this specific demographic which is applicable to urologists and patients alike.

This study showed no association between 5-ARI and the onset of depression and gynaecomastia within 6 months of commencing the medication. Unlike the results of this study, previous studies have reported increased risk of depression and gynaecomastia with the use of 5ARIs. A retrospective, matched-cohort study revealed an increased depression risk during the initial 18 months after the initiation of 5-ARI (HR=1.94; 95% CI= 1.73 to 2.16) [10]. An analysis between data from the Prostate Cancer Prevention Trial (PCPT), a 7-year prostate cancer prevention study, and Medicare claims, discovered that patients on finasteride had a 10% greater risk of new medical claims for depression when compared to non-users (HR=1.10, 95% CI = 1.01 to 1.19, *P* = .04) [11].

The PCPT Trial reported 4.5% of patients on finasteride experienced gynaecomastia compared to 2.8% of patients on placebo (*P* < .001; CRR=1.6) [12]. In the same way, the REDUCE Trial, a 4-year prostate cancer prevention study, reported gynaecomastia occurrence in 1.9% of dutasteride-treated patients compared to 1% of placebo-treated patients (*P* = .002; CRR=1.9) [13].

These studies which showed an increased risk of depression and gynaecomastia with 5-ARI use had a follow-up period of greater than 6 months, the shortest being 18 months; hence the follow-up period of 6 months in this study may have been too short to have shown a positive association. The potential mechanism that link 5-ARIs and depression include alteration in neuroactive steroids whilst gynaecomastia results from the conversion of excess testosterone to oestradiol by aromatase.

This study however, showed an effect of 5-ARI use on sexual function, particularly affecting the erection domain where there was a statistically significant (P = .05) reduction in the erection score within 6 months from baseline. This effect was seen regardless of the type of 5-ARI used; the erection score was reduced from 34.3 (sd 9.1) and 31.6 (sd 8.6) at baseline to 33.6 (sd 9.6) and 30.1 (sd 6.9) after commencing treatment for dutasteride and finasteride respectively. However, a clinically-relevant threshold for change in the MSHQ erection domain subscale has yet to be determined. The magnitude of change in the erection domain compared to baseline was considerable and was clinically correlated with 2 patients self-reporting erectile dysfunction as an adverse effect. A meta-analysis revealed that 5-ARI significantly increases the risk of erectile dysfunction in subjects with benign prostatic hyperplasia [OR = 1.47 (1.29; 1.68); P < .0001]. Additionally, the risk of erectile dysfunction was no different between finasteride and dutasteride [14]. These results are congruent with the findings of the present study. On the other hand, studies exist disputing a correlation between 5-ARIs and ED [15]. Due to the early reduction in MSHQ erection score, that is, within 6 months of commencing 5-ARI, this study implies that erectile dysfunction may be attributed to the medication and not to the natural decline in erectile function. The reduction of DHT levels and the shunting of testosterone to oestradiol caused by 5-ARIs elucidate their link to erectile dysfunction.

Drowsiness, bloating, insomnia and constipation were other self-reported adverse effects in this study. In no other studies however, were these symptoms characterized as adverse effects and cannot be explained by the pharmacology of the drug. Another finding of this study revealed that the proportion of patients who experienced personal stressors was lower after treatment compared with baseline, despite the negative effect on erectile function. This positive result could potentially be related to the likely improvement in their LUTS with 5-ARIs.

One limitation of this study is that the clinical significance of the observed change in the MSHQ erection subscale score is uncertain. Additionally, the study duration was 12 months, and the longest interval follow-up was 6 months, hence, the long-term adverse effects of 5-ARIs could not be evaluated. Nonetheless, the findings of this study demonstrate that erectile dysfunction is associated with 5-ARIs among patients with symptomatic BPH. Urologists should counsel their patients about the potential impact of 5-ARIs on sexual function before prescribing these medications and screen for these effects once these medications are commenced. Surgical management of BPH may need to be considered in patients experiencing adverse effects from these medications.

Conclusion

5-ARIs are associated with a reduction in MSHQ erection score within 6 months of therapy and may be correlated to the onset of erectile dysfunction.

Ethical Approval

Ethical approval was granted by the Ethics Committee for the respective institutions.

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