

Vulnerability of patients with prostatic hyperplasia treated with dutasteride and finasteride

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Summary

Benign prostatic hyperplasia is a pathology whose incidence has been increasing in recent years throughout Brazil. The disease is correlated with hormonal factors, and pharmacological treatment can have adverse effects on patients. This study assesses the socioeconomic and socio-cultural factors that interfere with healing or reduce quality of life. We analyzed data from Federal Government platforms between January 2009 and September 2019, looking at factors such as ethnicity, education level and economic status of patients. In all regions of Brazil, these factors proved to be important, as they can directly affect the incidence of the disease and adherence and continuity of treatment.

Keywords: Benign Prostatic Hyperplasia. Dutasteride. Finasteride. Social Vulnerability.

Resumo

Vulnerabilidade de pacientes com hiperplasia prostática tratados com dutasterida e finasterida

A hiperplasia prostática benigna é uma patologia cuja incidência vem crescendo muito nos últimos anos, em todo o Brasil. A doença está correlacionada a fatores hormonais, e o tratamento farmacológico pode gerar efeitos adversos nos pacientes. O objetivo deste estudo é avaliar fatores socioeconômicos e socioculturais que interferem na cura ou reduzem a qualidade de vida. Analisamos dados de plataformas do Governo Federal entre janeiro de 2009 a setembro de 2019, observando fatores como etnia, nível de escolaridade e situação econômica dos pacientes. Em todas as regiões do Brasil esses fatores se mostraram importantes, pois podem afetar diretamente a incidência da doença e a adesão e continuidade do tratamento.

Palavras-chave: Vulnerabilidade social. Hiperplasia prostática benigna. Dutasterida. Finasterida.

Resumen

Vulnerabilidad de pacientes con hiperplasia prostática tratados con dutasterida y finasterida

La hiperplasia prostática benigna es una patología cuya incidencia ha ido creciendo mucho en los últimos años, en todo Brasil. La enfermedad se correlaciona con factores hormonales, y el tratamiento farmacológico puede generar efectos adversos en los pacientes. El objetivo de este estudio es evaluar factores socioeconómicos y socioculturales que interfieren con la curación o reducen la calidad de vida. Analizamos datos de plataformas del Gobierno Federal entre enero de 2009 y septiembre de 2019, observando factores como el origen étnico, el nivel educativo y la situación económica de los pacientes. En todas las regiones de Brasil, estos factores demostraron ser importantes, ya que pueden afectar directamente la incidencia de la enfermedad y la adherencia y continuidad del tratamiento.

Palabras clave: Vulnerabilidad social. Hiperplasia prostática. Dutasterida. Finasterida.

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Social vulnerability is described as fragility, disadvantage, helplessness or abandonment. The concept is quite broad and encompasses various forms of social exclusion or isolation, from small to large groups. Vulnerability generally hinders or prevents the relationship with advancements, discoveries or benefits provided by technological development. In the context of research ethics, social vulnerability is understood by circumstances capable of affecting the quality of life of an individual or group regarding inclusion or exclusion in society¹⁻³.

In Brazil, between 2000 and 2010, social policies reduced poverty, increased the minimum wage and formalized work, among other actions. However, in recent years, social vulnerability and misery have increased in the country⁴⁻⁵. According to the Brazilian Institute of Geography and Statistics (IBGE), approximately 104 million Brazilians earn less than R\$413.00 per month, among whom 15.3 million live on less than R\$140.00 per month, in a situation of misery⁶.

In addition, approximately 73% of the poor in Brazil are black or brown, ethnic groups most vulnerable to pathologies such as systemic arterial hypertension, type 2 diabetes mellitus, human immunodeficiency virus, endocrine diseases and benign prostatic hyperplasia (BPH), among others⁷⁻⁸. Many of these pathologies are correlated with environmental and social factors and, among them, BPH has been growing exponentially in recent years.

BPH is a non-malignant disease characterized by an increase in epithelial and stromal tissues and a reduction in urinary flow, causing disorders known as "lower urinary tract symptoms". Recent evidence has shown the mechanisms that generate or control BPH. In addition, we know that aging is correlated with the disease, which currently affects approximately 50% of men over 50 years of age and 90% of men in the eighth decade of life⁹⁻¹².

One of the main lines of pharmacological treatment indicated by the American Urology Association and the European Urology Association is the prescription of 5-alpha-reductase inhibitors (5-ARI)¹³⁻¹⁴. 5-ARI prevents the conversion of testosterone and 5-alpha-androstenedione into dihydrotestosterone, which is the active form of testosterone, responsible for the development and progression of BPH^{11,15,16}. Treatment with these drugs decreases the proliferation of epithelial and stromal elements, reducing the volume of the

prostate by 20% to 30%, improving the quality of life of patients after 12 months of treatment¹⁷.

Currently, in Brazil, the 5-ARIs whose marketing is authorized by the National Health Surveillance Agency (Anvisa) are dutasteride and finasteride. Dutasteride has greater pharmacokinetic and pharmacodynamic effects than finasteride, as it inhibits the two isoforms of the 5-alpha-reductase enzyme (I and II), while finasteride only inhibits the type II isoform¹⁸.

Recent studies have shown that pharmacological treatment with 5-ARI for BPH can have adverse effects, such as erectile dysfunction and changes in renal morphology^{15,16,19-21}. However, despite all the adverse effects reported in the literature, the prescription of these drugs is still considered the best option for BPH treatment.

There are still no publications that discuss the vulnerability of Brazilian men to pharmacological treatment for BPH. Thus, this study makes a comparative analysis of the following data: number of men over 50 years old, endoscopic prostate resection surgeries performed, prostate biopsies, amounts spent on this procedure, illiterate population over 50 years, prices of reference drugs for the treatment of BPH and per capita income by ethnicity in all regions of Brazil.

Method

We analyzed the social profile according to the principlist theory and the concept of social vulnerability. In addition, we compared social vulnerability with the possible use of 5-ARI as a therapeutic approach for treating BPH. Data from the last 10 years were collected on the following data platforms of the Federal Government: Department of Informatics of the Brazilian National Health System (Datusus), Health Information (Tabnet), System of Management of Procedures Table, Drugs, Orthoses, Prostheses and Materials Specific to SUS (Sigtap) and IBGE.

The following data were compared: number of men over 50 years old, endoscopic prostate resection surgeries performed, prostate biopsies, amount spent on this procedure, illiterate population over 50 years old, prices of reference drugs for BPH treatment and per capita income by ethnicity in all regions of Brazil. The survey considered a period of

10 years (2009-2019), and the data were sorted out by the five regions of the country (North, Northeast, South, Southeast and Midwest). Data analysis and interpretation took place between October 2019 and January 2020.

In addition, we sought data from secondary sources: PubMed, Capes Periodicals and Scientific Electronic Library Online (SciELO). The keywords used were: “ethics based on principles”, “social vulnerability”, “bioethics”, “benign prostatic hyperplasia”, “dutasteride”, “finasteride” and their respective translations in Portuguese. The selected articles were included in the research according to their relevance in relation to the topic studied.

Discussion

According to the last IBGE census, Brazil has approximately 17,893,451 million men over 50 years of age. The region of the country with the highest concentration of this population group is the Southeast, with approximately 8,205,826 million men in this age group, and the lowest concentration is in the North^{22,23} (Table 1).

Recent studies describe that 50% of men over 50 years of age are likely to develop BPH^{10,11}. Prostate biopsy is one of the tools to prevent and aid in the diagnosis of BPH and prostate cancer; however, the number of such procedures performed in Brazil is still less than the number of possible BPH patients. According to data obtained from government platforms, approximately 435,154 prostate biopsies were performed from January 2009 to September 2019. In the last 10 years, the Brazilian National Health System (SUS) should have performed approximately 8,919,725 million prostate biopsies, the ideal number for preventing both BPH and prostate cancer according to the demand presented²³ (Table 1).

After BPH diagnosis, patients can undergo two types of intervention: surgical (endoscopic prostate resection) or pharmacological. In SUS, the amount referring to hospital service for endoscopic prostate resection is approximately R\$266.14, and the amount spent on professionals is R\$328.54, totaling an expense of approximately R\$594.68 per patient. Annually, the Ministry of Health invests around 7 billion BRL in surgeries of this type, but the values have not been readjusted

since 2009. The same is true for the number of surgeries approved by SUS, which apparently set a ceiling of approximately 12 thousand endoscopic prostate resections per year, distributed over the national territory disproportionately²³. Data from 2018 show that, of the 12,119 surgeries approved, 615 were performed in the North, 2,739 in the Northeast, 6,330 in the Southeast, 1,843 in the South, and 592 in the Midwest. Thus, the data show a high concentration of procedures in the Southeast region²³.

Due to the insufficient amount of prostate biopsies, which leads to late diagnoses, the pathology often progresses until lower urinary tract symptoms appear. In these cases, the clinical staff, considering factors such as the patient's age, may opt for pharmacological treatment, aiming at greater safety.

The price of 5-ARI varies across the five regions of Brazil: dutasteride costs between R\$90.22 and R\$385.56, and finasteride between R\$166.00 and R\$280.39²⁴. When comparing the cost of medications with income by ethnicity in Brazil, according to IBGE data, we observed that among blacks the average salary ranges from R\$368.78 to R\$680.06 per month, among whites from R\$679.31 to R\$1,267.25 per month, among Asians from R\$461.22 to R\$1,450.82 per month, and among browns from R\$414.98 to R\$696.85 per month^{22,23} (Table 1).

It is clear that the income gap between whites and blacks can make the beginning, adherence and completion of treatment unfeasible. Although they are more numerous in the Southeast region, where, theoretically, there is a greater technological and hospital subsidy, black individuals have the lowest salaries among different ethnicities. The problem is even more serious when considering that black men have a greater genetic predisposition to BPH, presenting the highest incidence of the disease among the entire population – which shows the vulnerability to which Brazilians are subjected.

There are also socio-cultural factors that can directly or indirectly influence treatment with 5-ARI, such as illiteracy and unemployment. According to the IBGE, Brazil currently has 11.3 million illiterates, a number that corresponds to approximately 6.8% of the population²⁵ (Table 1). Data published in 2019 on unemployment pointed to a 12.3% unemployment rate, equivalent to about 13 million Brazilians²⁶.

Table 1. Data analyzed from the Federal Government platforms

	North region	Northeast Region	Southeast region	South region	Midwest region
Male population (50 years onwards) [*]	1,092,926	4,481,275	8,205,826	2,907,457	1,205,967
Prostate biopsy ^a	18,216	59,364	231,832	96,402	29,340
Endoscopic prostate resection ^a	4,963	29,280	68,832	20,794	8,060
Illiterate population (50 years onwards) [*]	406,369	2,508,591	1,102,219	371,071	279,550
Gross domestic product (GDP) [*]	13041.58	9848.97	27141.92	22647.46	25253.47
Household per capita income of blacks (<i>reais</i>) [*]	421.12	368.78	579.72	580.32	680.06
Household per capita income of whites (<i>reais</i>) [*]	768.40	679.31	1,221.49	1,013.03	1,267.25
Household per capita income of browns (<i>reais</i>) [*]	414.98	366.02	581.64	556.43	696.85
Household income per capita of Asians (BRL) [*]	587.25	461.22	1450.82	1292.74	1103.77

^{*}Data from the last IBGE census, in 2010; ^adata from the period 2009-2019

The cost of medicines is incompatible with the average salary of most of the Brazilian population. Moreover, patients undergoing treatment with 5-ARI are prone to secondary pathologies: reduced libido, infertility, erectile dysfunction and renal failure. Importantly, not providing the patient with guidance on pharmacological treatment and its possible adverse effects is a risk factor that can directly affect the individual's quality of life.

In 2014, the pharmaceutical industry in Brazil achieved a record profit of US\$29.4 billion (about R\$123.2 billion), and the expectation is that in 2020 this turnover will reach US\$47.9 billion per year (about R\$200.7 billion). Brazil is among the six largest pharmaceutical markets in the world, and the growth is constant and exponential²⁷⁻²⁹. The data reveal the great commercial power of pharmaceutical companies in the country, which extends to scientific research, since this industry sponsors academic studies and has great influence on researchers, doctors and opinion makers. Thus, everything that is disclosed by the pharmaceutical market quickly begins to be claimed by patients in offices and hospitals, even leading to the judicialization of health¹.

With several adverse effects reported in the literature, some pharmacological treatment protocols have started to be developed. One of them combines 5-ARI with phosphodiesterase-5 enzyme inhibitors^{30,31}. This combination probably prevents changes in the corpora cavernosa caused by the isolated use of 5-ARI. However, studies indicate that, after treatment, there is a drastic reduction in the synthesis of nitric oxide, which is essential for the relaxation of the corpora cavernosa, generating erectile dysfunction²¹. In addition to these data, research shows that the combination of 5-ARI with phosphodiesterase-5 inhibitors causes more changes in the penis than the isolated treatment¹⁶.

In 2010, Anvisa authorized the marketing of another drug, which combines 5-ARI with alpha-1-adrenergic antagonists³². This new protocol would theoretically improve the symptoms of the lower urinary tract, reduce the volume of the prostate and avoid erectile dysfunction in patients^{30,33-35}. However, treatment with alpha-1-adrenergic antagonists has adverse effects such as depression, retrograde ejaculation and hypotension, among others^{36,37}.

Many studies have already reported changes in the urogenital system caused by 5-ARI, but little has been said about other adverse effects,



such as changes in renal morphology caused by the pharmacological treatment of reduced endothelial growth factor in the glomeruli, increased fibrosis in the renal medulla and Bowman's capsule, besides a considerable loss of nephrons^{19,20,38,39}. In addition, one should not lose sight of the fact that treatment can affect the patient's quality of life in the medium and long term.

Despite side effects, treatment with 5-ARI is still the most recommended, and should not be abandoned by patients until a new drug is developed with fewer adverse effects. However, there is difficulty in accessing treatment in the country, given the vulnerability of Brazilian men, relative to social, economic (cost of treatment) and ethical factors. It is important to note, however, that the 1988 Federal Constitution defines health as a right of all and a duty of the State, which is obliged to offer a free and quality health service to every Brazilian citizen. However, in practice, in the last four federal governments,

investments in SUS for the diagnosis and treatment of BPH have been insufficient⁴⁰. The social vulnerability of Brazilian men during or after treatment with 5-ARI can also influence the appearance of secondary pathologies.

Final considerations

Some studies have shown that treatment with 5-alpha-reductase inhibitors can cause morphophysiological changes. Treatment, however, remains the most recommended for patients with BPH. In Brazil, the financial resources of SUS to diagnose and treat this disease have not been readjusted for more than 10 years. The budget has proved to be insufficient in the face of greater demand, both for surgical intervention and pharmacological treatment. In this adverse scenario, there is an increasing development of secondary pathologies among vulnerable individuals.

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