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Original Scientific Paper

REVIEW OF ADVERSE DRUG REACTIONS OF MEDICINES USED FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA REPORTED TO HALMED

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SUMMARY – Benign prostatic hyperplasia is one of the most common diseases in men, with a prevalence rate of 50% in their 50s to 80% in their 80s, and is mostly treated with chronic drug therapy. The aim of this study was to analyze adverse drug reactions (ADR) to drugs used in benign prostate hyperplasia (BPH) treatment reported to HALMED from 2008 to 2021. Data on ADR reports in Croatia were obtained from the VigiFlow national database and on the use of drugs for BPH in Croatia from Drug Utilization Reports from HALMED. In the observed period, the number of reports on each BPH drug, total number of reports, seriousness of reported ADR, patient age and sex, type of reporter, and most reported ADRs were analyzed. Results showed that 438 ADR reports were received, of which 45.95% on tamsulosin as the most frequently used drug for BPH. Of all reports, 84% were non-serious, 96% were reported in men and 82% in patients older than 45 years. The most frequently reported ADRs were consistent with the known safety profile of BPH drugs. Pharmacists were the most common (47%) reporters of ADRs for BPH drugs, while 33% were reported by physicians. Analysis of the reported ADRs showed that most frequently reported ones were in line with the known safety profile of BPH drugs. However, given the prevalence of the disease and the extent of the use of BPH drugs, it could be argued that the number of reports could be higher (i.e., 34 reports/year). Reporting on ADRs is necessary to better understand the safety profile of drugs in the post-authorization period, and more information on the safe use of medicines could be collected by raising awareness of healthcare professionals.

Key words: *Benign prostate hyperplasia; Tamsulosin; Silodosin; Doxazosin; Finasteride; Dutasteride; Serenoa repens extract; Tadalafil; Combination of tamsulosin and solifenacin; Combination of tamsulosin and dutasteride; Side effects*

Introduction

Benign prostate hyperplasia (BPH) is one of the most common diseases among men aged 40 years and older[1], with a prevalence rate of 50% in their 50s to 80% in their 80s[2]. BPH is mostly treated with chronic drug therapy[1,3].

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Agency for Medicinal Products and Medical Devices of Croatia (HALMED) was established in 2003, and since 2005 it has become the Croatian National Center for Monitoring Adverse Drug Reactions (ADR) and is responsible for collecting ADRs of drugs used in Croatia, which have been observed after drug administration, but not necessarily caused by a drug[4]. Under the new Medicines Act from 2007, healthcare professionals and marketing authorization holders are legally obliged to report ADRs to HALMED, but they can also be reported by patient or patient's

parent or another caregiver. Any report submitted to HALMED is considered a suspected ADR. Following administrative editing of the report, seriousness and causal relationship between the reported reaction and drug is assessed, in accordance with current legislation and international assessment criteria established by the World Health Organization (WHO)[5,6]. The reports are entered in the Croatian ADR database (VigiFlow) and forwarded to the European ADR database EudraVigilance and WHO ADR database VigiBase. All reports are part of the drug safety documentation.

According to the WHO Anatomical Therapeutic Chemical (ATC) Classification, drugs used in the treatment of BPH are classified in category G04C, which consists of the following drug groups: alpha-adrenoreceptor antagonists, testosterone-5-alpha reductase inhibitors, and other drugs used in BPH[7].

Their use is on a significant and continuous increase, primarily tamsulosin as the most commonly used one, but also finasteride as the second most frequent, according to the Drug Utilization Reports published annually and periodically by HALMED[8].

The aim of this study was to analyze ADRs to BPH drugs reported to HALMED from 2008 to 2021. Although the usage of BPH drugs has been continuously increasing and given the prevalence of the disease, the number of received ADR reports could have been higher than the current 34 reports/year. The most frequent reporters of ADRs for BPH drugs were pharmacists. It could be argued that raising awareness among prescribing physicians could lead to increasing the number of ADR reports and better understanding of the safety profile of BPH drugs.

Methods

The HALMED Medicinal Products Database[9] was searched on April 20, 2022 to extract in the form of an Excel spreadsheet data on BPH drugs approved in Croatia, which are listed according to their active substance.

Drugs used for BPH treatment are alpha-adrenoreceptor antagonists (tamsulosin, silodosin, doxazosin, combination of tamsulosin and solifenacin, combination of tamsulosin and dutasteride), testosterone-5-alpha reductase inhibitors (finasteride, dutasteride), and other drugs (*Serenoa repens* extract, tadalafil).

The national ADR database VigiFlow was searched with the criterion "G04C" and data were extracted into a spreadsheet. The number of reports over time was reviewed, and the period from January 1, 2008 to December 31, 2021 was chosen as an additional filter because of the availability and quality of data, and reports *per* drug for BPH, patient age and sex, type of reporter and most commonly reported ADRs were analyzed. For drug nomenclature in VigiFlow, the WHO Drug Dictionary was used, which is regularly updated regarding active ingredient nomenclature and WHO ATC Drug Classification. In several cases, active ingredient is listed in VigiLyze in more than one active ingredient variant (tamsulosin hydrochloride and tamsulosin, doxazosin mesylate and doxazosin, *Serenoa repens* extract and *Serenoa repens*). A number of reports and adverse drug reactions for tamsulosin, doxazosin and *Serenoa repens* extract were summed up from numbers for each active ingredient variant. Age groups in VigyLyze were set according to the GVP Module VI guidelines[6].

Adverse drug reaction nomenclature and classification in organ classes were coded in line with Medical Dictionary for Regulatory Purposes, developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) to facilitate sharing of regulatory information internationally.

Drug Utilization Reports from HALMED were analyzed for trends in the use of drugs for BPH from 2008 to 2020. Report for the year 2021 was not yet available. *Serenoa repens* extract is not included in Drug Utilization Reports. The unit for drug use was defined as the Defined Daily Dose *per* 1000 inhabitants *per* day (DDD)/1000/day), according to the WHO ATC/DDD Methodology[10].

Data collected in this study were analyzed by descriptive statistics. Quantitative variables were expressed as numbers or percentages and shown in the form of tables and figures.

Results

Number of ADR reports for BPH drugs submitted to HALMED

From 2008 to 2021, 438 reports of ADRs to BPH drugs were submitted to HALMED. The number of reports for BPH drugs received annually is shown in Figure 1.

The number of reports for each BPH drug is shown in Figure 2. Total number of reports on BPH drugs (n=444) is higher than the total number of reports (n=438) because it is possible to list one or more drugs suspected to cause ADR in one report.

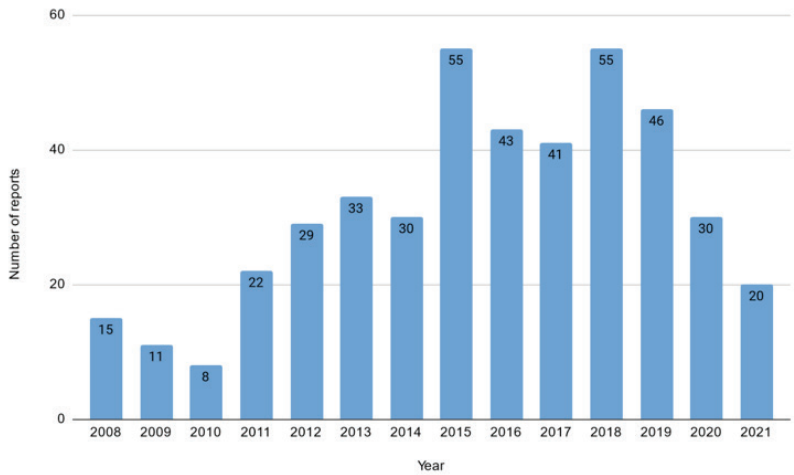

Fig. 1. Number of adverse drug reaction (ADR) reports for benign prostate hyperplasia (BPH) drugs submitted to HALMED from 2008 to 2021.

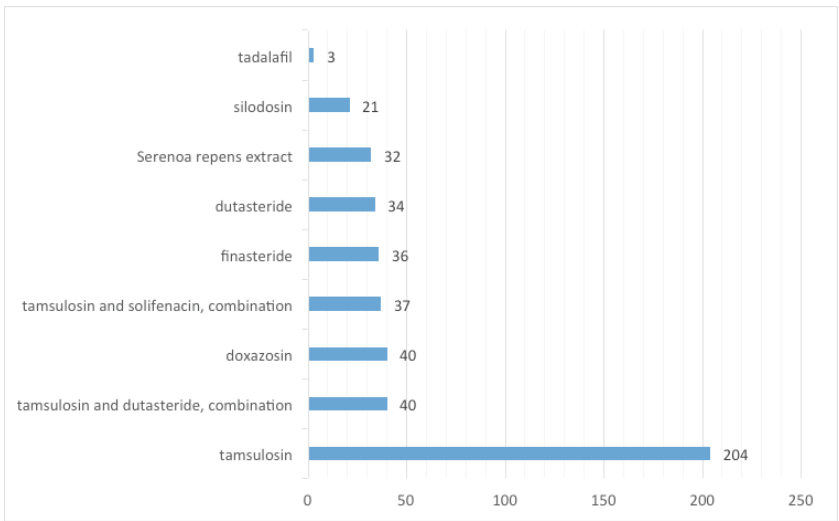

Fig. 2. Number adverse drug reaction (ADR) reports for each benign prostate hyperplasia (BPH) drug.

Seriousness of reported ADRs for BPH drugs

Out of the total number of reports, 83.6% (366 reports) were assessed as non-serious, 13.5% (59 reports) were assessed as serious, and for 3.0% (13 reports) seriousness was unknown, as shown in Figure 3. Reports that were assessed as serious met the following criteria: in 1 (1.1%) report, ADR was life-threatening (suspected angioedema due to tamsulosin), in 9 (15.3%) reports, ADRs caused or prolonged hospitalization, and in 45 (76.3%) reports, ADRs were classified as other medically important condition. Since more than one seriousness criterion can be selected in a report, their number may exceed the number of reports.

Patient age and sex distribution

Male gender was recorded in 420 (95.9%) reports, female gender in 13 (3.0%) reports, and in 5 (1.1%) reports it was unknown (not reported). Distribution of reports according to patient age is shown in Figure 4.

Type of reporter

Distribution of reports according to reporter qualification is shown in Figure 5.

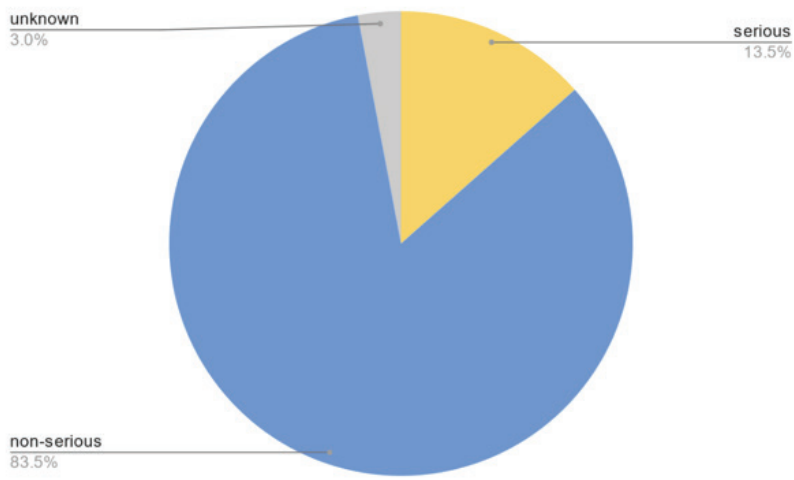

Fig. 3. Seriousness of reported adverse drug reactions (ADRs) for benign prostate hyperplasia (BPH) drugs.

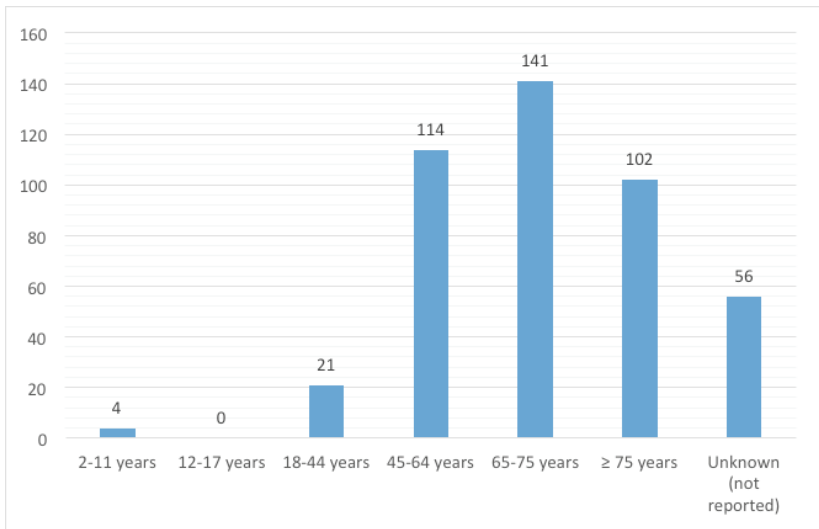

Fig. 4. Patient age distribution in adverse drug reaction (ADR) reports for benign prostate hyperplasia (BPH) drugs.

The most commonly reported ADRs for BPH drugs

The most commonly reported ADRs for BPH drugs are shown in Figure 6. The most commonly reported ADRs for tamsulosin were dizziness, pruritus, vertigo, headache and nausea; for the combination of tamsulosin and dutasteride, dizziness, pruritus, headache, hypotension and visual impairment; for doxazosin, headache, dry mouth, cough, vertigo and blood pressure decreased, fatigue, pruritus and tinnitus; for the combination of tamsulosin and solifenacin, dry mouth, urinary retention, pruritus, constipation, dizziness and rash; for finasteride, gynecomastia, rash, decreased libido, visual impairment and erectile dysfunction; for dutasteride, dysuria, gynecomastia, fatigue, arrhythmia and breast pain; for *Serenoa repens* extract, dyspepsia, constipation, blood in urine, abdominal discomfort, upper abdominal pain and pruritus; for silodosin, diarrhea, dizziness, erythema, erectile dysfunction and dyspnea; and for tadalafil, abdominal pain, back pain, dizziness, head discomfort, headache, prostatomegaly, ocular discomfort and intentional product misuse.

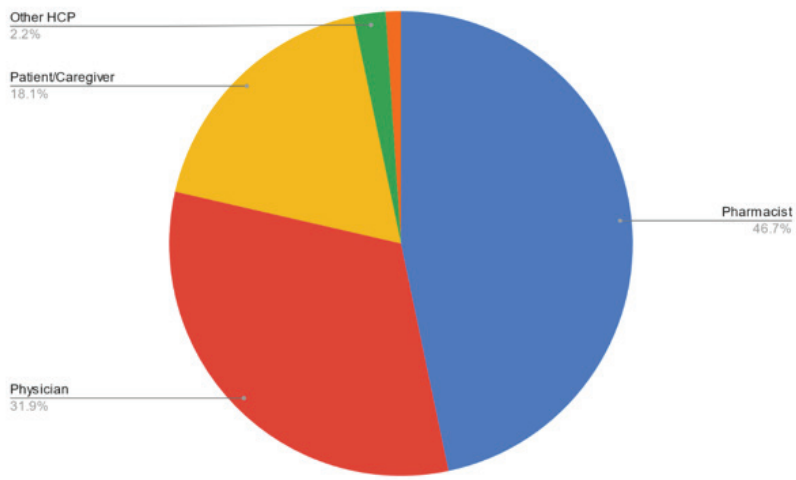

Fig. 5. Contribution of type of reporter in total number of adverse drug reactions (ADRs) for benign prostate hyperplasia (BPH) drugs.

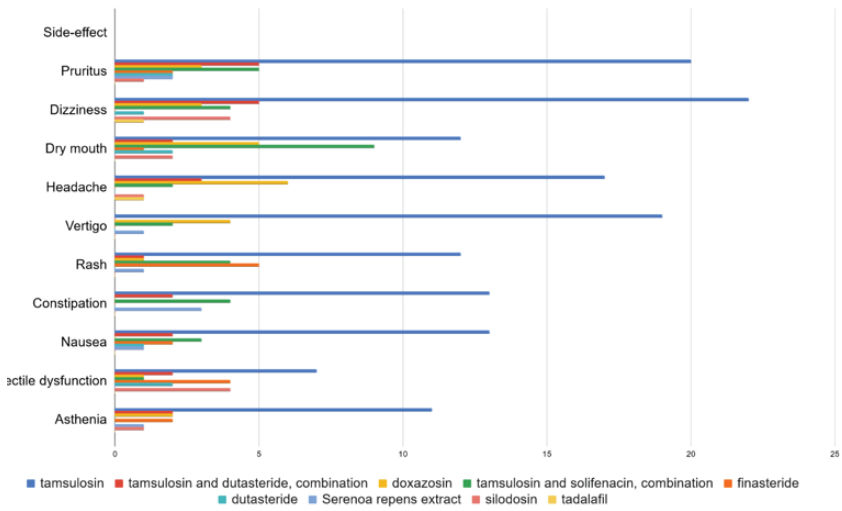

Fig. 6. Ten most frequently reported adverse drug reactions (ADRs) for benign prostate hyperplasia (BPH) drugs.

Use of BPH drugs in Croatia

From 2008 to 2020, the use of drugs for BPH was continuously growing; cumulatively for all of them, it increased 4.44 times (from 5.66 to 25.15 DDD/1000/day). The use of drugs for BPH in Croatia *per* drug is shown in Figure 7.

Discussion

From 2008 to 2021, 438 ADR reports on BPH drugs were submitted to HALMED, i.e., 34 reports/year. The highest number of reports (n=55) was received in 2015 and 2018. From 2019, the number of reports was slightly declining, and in 2021 only 20 were received, which can be explained by the COVID-19 pandemic, which greatly affected the healthcare system in general, including urology[11]. The highest number of reports was received for tamsulosin (45.95%), possibly because tamsulosin is more commonly prescribed than other drugs used to treat BPH. According to the European Association of Urology Guidelines, the level of evidence for alpha-adrenoreceptor antagonist is 1a, which is highest in this group of drugs[3]. Dahm *et al.*

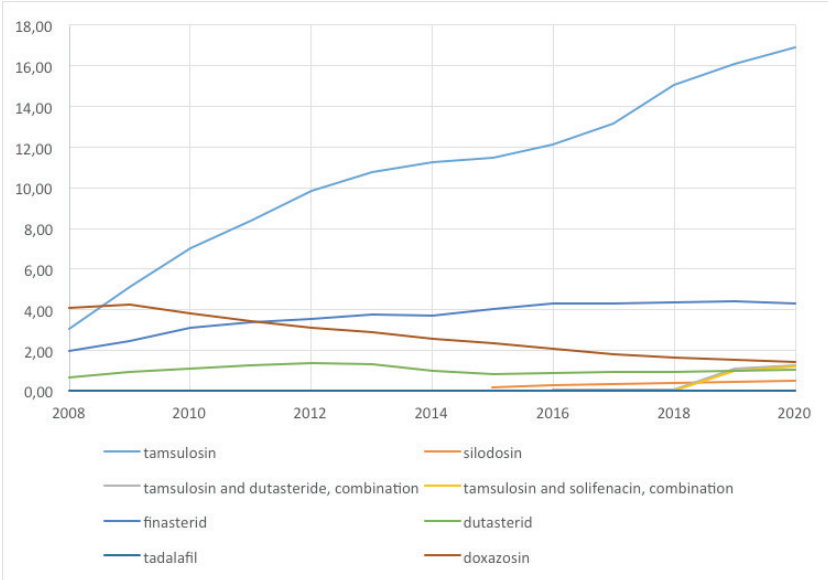

Fig. 7. Use of benign prostate hyperplasia (BPH) drugs in Croatia in Defined Daily Dose per 1000 inhabitants per day (DDD/1000/day).

report that traditional treatment with alpha-blockers showed superior results in treating lower urinary tract symptoms (LUTS) in men compared to other drugs or their combinations[12]. According to Drug Utilization Reports from HALMED, from 2008 to 2020 the use of drugs for BPH increased 4.44 times, with tamsulosin as the most widely used drug[8]. For other drugs or their combinations (combination of tamsulosin and dutasteride, doxazosin, combination of tamsulosin and solifenacin, finasteride, dutasteride, *Serenoa repens* extract, silodosin), the number of reports ranged from 21 for silodosin to 40 for the combination of tamsulosin and dutasteride, and for doxazosin. Several drugs from this group have not been authorized in Croatia during the entire observed period, such as the combination of tamsulosin and dutasteride that was authorized in 2011, the combination of tamsulosin and solifenacin in 2014, silodosin in 2012, and tadalafil in 2012. Doxazosin is authorized for both hypertension and BPH and currently belongs to the ATC group of antihypertensives[7], and although no longer prescribed for BPH alone, it has found its clinical application in patients with concomitant hypertension[13]. Tadalafil is authorized for both erectile dysfunction and BPH, and currently belongs to the ATC group of drugs used in erectile dysfunction[7]. Three reports were received for tadalafil, in which indication was not reported.

The majority (83.5%) of BPH drug ADR reports were assessed as non-serious, while 13.5% of reports assessed as serious met at least one of the following criteria: life-threatening, caused or prolonged hospitalization, or classified as other medically important condition. Since reports may have more than one severity criterion, the number of criteria selected may exceed the number of reports. Related to the life-threatening criterion, the suspected drug was tamsulosin, and ADR was angioedema. In 9 reports with the caused/prolonged hospitalization criterion, multiple concomitant drugs and underlying diseases were reported. The other medically important condition criterion may refer to a medical term listed in the list of Important Medical Events[14], or may be indicated by the reporter.

Since the incidence of BPH increases significantly with age, it is important to show the relationship between patient age and reported ADRs[15]. The majority (81.5%) of reports were received for the group of patients aged 45 and over, 4.8% for patients aged 18 to 44, and 0.9% for children aged 2 to 11. All 4 reports for children were received from the Poison Control Center, Institute for Medical Research and Occupational Health, with a report of accidental exposure to a product by child. In 12.8% of reports, patient age was not reported (unknown). In 95.9% of the reports, patient sex was male and in 3.0% female, and their re-

ports related to doxazosin and tamsulosin. In 1.1% of the reports, patient sex was not reported (unknown). Doxazosin is also used for hypertension, and tamsulosin for ureterolithiasis in both men and women[16]. Since drugs for BPH are most often prescribed to men aged 40 and over, the age distribution in ADR reports is consistent with the frequency of using these drugs for BPH or male LUTS.

As for the reports themselves, most often, i.e., in 47% of cases, ADRs were reported by pharmacists, in 32% by physicians, in 18% by patients or caregivers, and in 3% by other healthcare professionals. Given that all BPH drugs except for *Serenoa repens* extract are only available on prescription, it could be concluded that raising awareness of ADRs among prescribing physicians could lead to more reports.

The most commonly reported ADRs for BPH drugs were pruritus, dizziness, dry mouth, headache, vertigo, rash, constipation, nausea, erectile dysfunction, and asthenia, which is consistent with the known safety profile of BPH drugs, according to the information shown in approved product information[9].

In conclusion, although the use of drugs for BPH is continuously increasing, the number of ADR reports increased until 2018, and has been steadily declining since then. Most of the ADRs were non-serious and were in line with the known safety profile of BPH drugs. The highest number of reports was received for tamsulosin, which could be due to the wide use of tamsulosin in comparison to other drugs for BPH. Pharmacists were the most common reporters of ADRs for BPH drugs. It is likely that raising awareness among physicians could lead to an increasing number of ADR reports and better understanding the safety profile of drugs for BPH.

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Sažetak

ANALIZA PRIJAVA SUMNJI NA NUSPOJAVE LIJEKOVA ZA LIJEČENJE BENIGNE HIPERPLAZIJE PROSTATE PRIJAVLJENE HALMED-u

I. Kuliš, Ž. Margan Koletić, T. Hudolin i *S. Tomić*

Benigna hiperplazija prostate (BHP) jedna je od najčešćih bolesti u muškaraca dobi od 50 godina i više, s učestalošću od 50% do 80% u muškaraca starijih od 80 godina. Danas se najčešće liječi kroničnom terapijom lijekovima. Cilj ovoga rada bio je analizirati prijave sumnji na nuspojave lijekova za liječenje BHP prijavljene Agenciji za lijekove i medicinske proizvode (HALMED) od 2008. do 2021. godine. Podaci o prijavama izdvojeni su iz nacionalne baze nuspojava VigiFlow. Analiziran je ukupan broj prijava za lijekove za BHP, broj prijava za svaki lijek za BHP, ozbiljnost prijavljenih nuspojava, dob i spol bolesnika, vrsta prijavitelja i najčešće prijavljene nuspojave. Podaci o potrošnji lijekova izdvojeni su iz HALMED-ovih Izvješća o potrošnji lijekova u Republici Hrvatskoj. U promatranom razdoblju zaprimljeno je 438 prijava sumnji na nuspojave lijekova koji se primjenjuju u liječenju BHP-a, od čega je najviše prijavljeno za tamsulozin (45,95%), koji je i najčešće primjenjivani lijek za BHP. Od ukupnog broja prijava 83,5% prijava je bilo ne-ozbiljne naravi, 95,9% je prijavljeno u muškaraca, a 81,5% prijava prijavljeno je u bolesnika u dobi od 45 godina i više. Najčešći prijavitelji bili su farmaceuti (u 46,7% prijava). Liječnici su prijavili 32,9% prijava. Najčešće prijavljivane nuspojave u skladu su s poznatim sigurnosnim profilom lijekova za BHP. Međutim, uzimajući u obzir učestalost BPH i čestu primjenu farmakoterapije u liječenju BPH moglo bi se zaključiti da bi broj prijava mogao biti veći od sadašnje 34 prijave godišnje. Prijavljivanje sumnji na nuspojave nužno je za bolje razumijevanje sigurnosnog profila lijekova nakon stavljanja u promet. Podizanjem svjesnosti svih zdravstveni djelatnika o važnosti prijavljivanja nuspojava može se doprinijeti prikupljanju veće količine informacija i ukupnom znanju o sigurnoj primjeni lijekova.

Ključne riječi: *Benigna hiperplazija prostate; Tamsulozin; Silodosin; Doksazosin; Finasterid; Dutasterid; Ekstrakt Serenoa repens; Tadalafil; Tamsulozin i dutasterid; Tamsulozin i solifenacin; Nuspojave*