Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) is one of the most common urinary disorders in elderly men. In recent years, pharmacotherapy of BPH has increased the efficacy, including combination treatment mostly with two drug classes, namely, 5α-reductase inhibitors and α-1-adrenolytics (alpha blockers) with a different pharmacological activity. Although pharmacological treatment of BPH is a success story in urology, daily practice suggests that several medical needs remain unmet. We aimed to evaluate drug adherence in patients receiving pharmacological therapy to treat LUTS/BPH, and to analyze drug adherence among monotherapy and combination therapy. The sample population consisted of 758 men aged ≥40 years who had been prescribed medications for LUTS/BPH during the index period between June 2015 and August 2016. Only alpha blockers and 5α-reductase inhibitors (5ARIs) were considered in the analysis. Among ABs there were doxazosin, tamsulosin, alfuzosin, terazosin and among 5α-reductase inhibitors it was only finasteride. Drug adherence was assessed in patients who were treated for a minimum of 6 months. Two levels of exposure were evaluated, follow-ups: ≥6 months, and ≥12 months. In patients who were treated for at least 6 months, the drug adherence rate was 32% and the 12-month drug adherence rate was 23%. We observed an inverse relationship between drug adherence rates and the duration of treatment - longer the duration of pharmacological therapy, lower was the drug adherence rate noted. Our study shows a low rate of overall drug adherence in patients diagnosed with BPH. It was observed that a low adherence rate is closely related to drug-related problems (DRP). Furthermore, this is a correlation between the degree of LUTS/BPH and adherence rate - the higher degree of LUTS/BPH, the higher adherence rate. Further studies are warranted focusing on assessing adherence to pharmacological therapy.

**Key words:** urinary tract, prostatic hyperplasia, patient compliance, medication adherence, drug therapy, 5-alpha-reductase inhibitors, alpha-1-adrenolytics

**INTRODUCTION**

One of the most common urinary disorders in elderly male population is lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). The symptoms of this disease entity are bladder outlet obstruction, prostate gland enlargement, and lower urinary tract symptoms (1). BPH contributes to bladder infections and stone formation of the bladder and the risk of urinary retention significantly increases causing renal failure (2, 3). Due to the increasing life expectancy of men, this disease entity relates to relevant implications within diagnostics, therapy and socioeconomics. BPH often requires surgical treatment (4); however, in recent years, fewer surgical interventions are being performed owing to the proven efficacy of pharmacotherapy, including combination treatment that primarily uses 2 classes of drugs, 5α-reductase inhibitors (5ARIs) and α-1-adrenolytics (alpha blockers (ABs)) with a different pharmacological activity (4). The α-1-adrenolytic class manages urinary symptoms by improving objective parameters such as by increasing the maximum urine flow rate, and decreasing urinary retention after micturition (1). Noradrenaline acts on the α-1-adrenergic receptors (α-1-ARs) located in the neck and sphincter of the urinary bladder to promote contraction and prevent urinary retention and also controls the smooth muscles in the capsule of prostate and prostatic urethra. Selective α-1-AR blockers relax smooth muscles in the prostate and bladder neck causing relief of obstruction (1, 5).

Long-term combination therapy (CT) using ABs and 5α-reductase inhibitors (5ARIs) is beneficial in terms of symptom control and disease progression (6, 7).

Pharmacotherapy of BPH is very effective in urological clinical practice; however, there remain several unmet medical needs, such as limited drug effectiveness, low drug adherence, or inappropriate patient management (8-10). Several medical needs such as limited drug effectiveness secondary to low drug adherence or inappropriate patient management could be met based on the results of this study, which analyses the reasons for this observation. A greater focus on the physician-patient relationship and communication is important to improve the effectiveness of pharmacological therapy. Furthermore, the correlation between long-term treatment and drug adherence and BPH progression has not yet been completely researched.
and drug-related problems (DRPs). In this study, it was assessed that multiple medications have got a significant impact on adherence, indicating a crucial role of the fixed dose combination which might improve drug adherence (13).

Data regarding adherence are vital to understand possible unmet needs, to explore patient preferences, and to identify possible areas in healthcare systems that could benefit with intervention (14, 15). The WHO defines adherence as ‘the extent to which the persons’ behavior (including medication-taking) corresponds with agreed recommendations from a healthcare provider’ (16).

Our study aimed to demonstrate the importance of drug adherence and the need of increased patient awareness regarding their drug regimens. The results of this study will help clinicians to identify areas of drug regimens that present difficulties and strategies to eliminate these difficulties.

We aimed to evaluate drug adherence in patients receiving pharmacological therapy to treat LUTS/BPH, and to analyze drug adherence among monotherapy and combination therapy.

MATERIAL AND METHODS

This retrospective study was conducted using a database of patients in two urological clinics. The urologists have got a full access to general database. The sample population consisted of 758 men aged ≥ 40 years who had been prescribed medications for LUTS/BPH during the index period between June 2015 and August 2016. The patients were prescribed finasteride at a dosage of 5 mg/day owing to BPH and urinary dysfunctions. In addition, the combination therapy of finasteride and other alpha-1-adrenolitics consists of the following: alfuzosin (10 mg/day), doxazosin (4 or 6 mg/day), tamsulosin (0.4 mg/day), and terazosin (10 mg/day).

In patients older than 45 years with hypertension, sexually active, without cardiac co-morbidities, doxazosin was used which does not cause any sexual disorders. Tamsulosin was used in patients aged > 55 years, with low blood pressure, after cardiac surgeries. The above-mentioned drugs are effective because they decrease dysuric discomforts, improve objective parameters, increase maximum flow rate, and decrease residual urine. We analysed the role of ABs (doxazosin, tamsulosin, alfuzosin and terazosin) and 5ARIs (finasteride). The baseline severity of LUTS/BPH was assessed using IPSS value. The mean IPSS value during the first appointment was 24 which mean the presence of severe symptoms.

Drug adherence was assessed in patients who were treated for a minimum of 6 months. Two levels of exposure were evaluated, follow-ups: ≥ 6 months, and ≥12 months.

The Medication Adherence Questionnaire (MAQ) was used to assess drug adherence in patients with LUTS/BPH. This scale contains 4 questions with ‘Yes’ or ‘No’ response choices. The total score ranges between 0 and 8 with lower scores reflecting better medication adherence. Scores of ≥ 3 indicate low adherence, scores between 1 and < 2 indicate moderate adherence, and a score = 0 indicates high adherence (17). The MAQ was completed twice by patients during the 6- and 12-month follow-up. The Charlson comorbidity index (CCI) score adapted to The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) was used as a measure of comorbidities (18). Furthermore, we analysed the following data: mean age, duration of pharmacotherapy administered for BPH, type of pharmacotherapy (AB, 5ARI, or CT), comorbidities, drug adherence, causes of non-adherence, and drug-related problems (DRPs). In this study, it was assessed a role of drug-related problems (DRPs) which play a crucial role in non-adherence. Factors contributing to non-adherence could be identified as those related to patients, treatment or health care providers such as patients not considering that treatment as necessary, a complex treatment regimen that increased the risk of non-adherence, inappropriate physician-patient, as well as DRPs. Multivariate regression was applied to assess patient factors and adherence rate. Multivariate analysis of variance (MANOVA) with adherence rate as outcome variable and the patient factors as indicator variables were used for data analysis.

In patients who received at least 12 months of treatment, characteristics were reported using descriptive statistics. Differences between patient treatment subgroups were assessed using a standardised difference.

All statistical analyses were performed using the Stata/IC 14.2 software. The Student’s t-test was used to analyse differences in adherence rates observed during 6- and 12-month follow-up. For all Cox models, the associations between groups and all outcomes were adjusted for covariates known to be of prognostic significance for the outcomes analysed: age, CCI. Results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

According to the Act of 6 September 2001 Pharmaceutical Law, the study was qualified as noninterventional observation study. It means that 1) the treatment’s products will be used in the way, which determines the marketing authorization; 2) qualification of patient to the group which uses a specific treatment’s strategy does not result based on study protocol but it will be achieved according to current medical practice; 3) any additional diagnostic procedures and monitoring procedures will not be used against the patient. Moreover, the researchers did not transfer the personal data of observed patients to the organizer. Thus, this study did not require approval by Ethics Committee and registration in Central Register of Clinical Studies.

RESULTS

Our study population consisted of 670 men aged ≥ 40 years. We excluded 88 (11.61%) patients who discontinued use of pharmacological therapy, drug adherence was assessed in patients who were treated for a minimum of 6 months. The shorter time of treatment was synonymous with exclusion from the study within the first 6 months of the study. The patients included in the study had not any previous prostate surgeries, adenectomy, transurethral resection of the prostate (TURP) or laser photoselective vaporization prostatectomy (PVP). They had a diagnosis of BPH for 5 – 15 years.

General characteristics of patients have been reported in Table 1 which shows adherence rate in patients with no additional diseases, with 1 – 2 diseases or > 3 diseases, therefore CCI score was helpful in assessing polypharmacy within adherence rate.

The mean age of patients was 72.5 years (standard deviation 8.48 years). We observed that 368 patients (54.92%) showed a CCI of 1 – 2, 248 patients (37.01%) showed a CCI of > 3, and 54 patients (8.05%) showed a CCI of 0. The most common comorbidities were: hypertension (70%), coronary disease (40%), diabetes (20%), peptic ulcer disease (15.07%), and chronic obstructive pulmonary disease (COPD) (7.01%) (Fig. 1). In the group of patients aged 40 – 55 years, the most frequent disease was hypertension and peptic ulcer disease, in the group of patients aged 56 – 65 years, hypertension, COPD and diabetes, in the group of patients aged 66-75 years, hypertension, coronary disease and diabetes. The minimum and maximum total prostate volume (TPV) was 38 mL and 76 mL, respectively.

α1-adrenolytics confirmed high efficiency because decreased
dysuric discomforts and residual urine after miction, and increased maximum flow rate. The most efficient α₁-adrenolytics were doxazosin and tamsulosin, especially within a significant improvement of maximum flow rate (Qmax) and time of miction (T flow), and within decreasing residual urine after miction (Rv). Two levels of exposure were assessed, follow-ups after 6 and 12 months.

The follow-up results after 6 months were as follows:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>AB</th>
<th>5ARI</th>
<th>CT</th>
<th>After 6 months</th>
<th>After 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>670</td>
<td>182 (27.16%)</td>
<td>35 (5.22%)</td>
<td>453 (67.61%)</td>
<td>217 (32.38%)</td>
<td>157 (23.43%)</td>
</tr>
<tr>
<td>Mean age/years (SD)</td>
<td>72.5</td>
<td>65.5</td>
<td>73.0</td>
<td>79.0</td>
<td>70.5</td>
<td>72.0</td>
</tr>
<tr>
<td>Age, n, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 – 55</td>
<td>22 (3.28%)</td>
<td>2 (0.29%)</td>
<td>4 (0.59%)</td>
<td>16 (2.38%)</td>
<td>13 (5.99%)</td>
<td>17 (10.82%)</td>
</tr>
<tr>
<td>56 – 65</td>
<td>111 (16.56%)</td>
<td>38 (5.67%)</td>
<td>7 (1.04%)</td>
<td>66 (9.85%)</td>
<td>22 (10.13%)</td>
<td>23 (14.64%)</td>
</tr>
<tr>
<td>66 – 75</td>
<td>305 (45.52%)</td>
<td>71 (10.59%)</td>
<td>11 (1.64%)</td>
<td>223 (33.28%)</td>
<td>87 (40.09%)</td>
<td>62 (39.49%)</td>
</tr>
<tr>
<td>76 – 85</td>
<td>178 (26.56%)</td>
<td>55 (8.20%)</td>
<td>7 (1.04%)</td>
<td>116 (17.31%)</td>
<td>72 (33.17%)</td>
<td>41 (26.11%)</td>
</tr>
<tr>
<td>&gt; 85</td>
<td>54 (8.05%)</td>
<td>16 (2.38%)</td>
<td>6 (0.89%)</td>
<td>32 (4.77%)</td>
<td>23 (10.59%)</td>
<td>14 (8.91%)</td>
</tr>
<tr>
<td>Charlson score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>54 (8.05%)</td>
<td>13 (7.14%)</td>
<td>27 (77.14%)</td>
<td>14 (3.09%)</td>
<td>57 (29.38%)</td>
<td>36 (13.09%)</td>
</tr>
<tr>
<td>1 – 2</td>
<td>368 (54.92%)</td>
<td>79 (43.40%)</td>
<td>3 (8.57%)</td>
<td>286 (63.13%)</td>
<td>87 (44.84%)</td>
<td>118 (42.90%)</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>248 (37.01%)</td>
<td>103 (56.59%)</td>
<td>5 (14.28%)</td>
<td>140 (33.77%)</td>
<td>50. (25.77%)</td>
<td>121 (44%)</td>
</tr>
</tbody>
</table>

AB, alpha blocker monotherapy; 5ARI, 5-α-reductase inhibitor monotherapy; CT, combination.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Drug adherence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
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<td>65.5</td>
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AB, alpha blocker monotherapy; 5ARI, 5-α-reductase inhibitor monotherapy; CT, combination.

The mean IPSS value during the first appointment was 24, and after 12 months the IPSS value was 11.
The adverse effects were observed in 30% after combination of drug therapy. The most common adverse effects were reported in patients using doxazosin and included mainly orthostatic hypotension, palpitations and arrhythmia. In patients using alfuzosin, the most often adverse effects were orthostatic hypotension and stomachache. In the group of patients using terazosin, the following adverse effects were present, orthostatic hypotension and palpitations. The least number of adverse effects were present in the group using tamsulosin, and the following adverse effects were observed, retrograde ejaculation and decreased ejaculation or anejaculation.

CT was the most frequently prescribed drug regimen (67.61%) followed by AB (27.16%) and 5ARI (5.22%). Among alpha-1-adrenolytics, the most frequently used drug were tamsulosin and doxazosin.

In patients who were treated for at least 6 months, the drug adherence rate was 32% and the 12-month drug adherence rate was 23% (Fig. 2). We observed an inverse relationship between drug adherence rates and the duration of treatment.

**Table 1. Patients characteristics according to BPH/LUTS.**

**Fig. 1. Comorbidities in patients with BPH/LUTS.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Drug adherence</th>
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<td>65.5</td>
</tr>
</tbody>
</table>
the longer was duration of pharmacological therapy, the lower was the drug adherence rate noted. The same relationship between the number of adherent patients and groups of drugs was observed over 2 follow-up periods. At the 6-month follow-up we observed that the number of patients who showed drug adherence was: AB (8.50%), 5ARI (2.08%), and CT (21.79%) (Fig. 3).

In this study, it was also analysed a relationship between the degree of LUTS/BPH and adherence rate during the 6- and 12-month follow-up. The follow-up results after 6 months were as follows: drug adherence in mild symptoms - 26%, moderate - 34%, severe - 36%. The follow-up results after 12 months were as follows: drug adherence in mild symptoms - 16%, moderate - 25%, severe - 28%.

During the follow-up period, we observed that 670 patients (88.39%) continued pharmacological therapy, and the therapy discontinuation rate was 11.61%.

We identified 230 DRPs (drug-related problems) in this study during follow-up visit after 6 months. The top three categories of DRPs observed were drug problems (37.39%), drug use process (23.04%), adverse reactions (20.86%), and drug choice problems (18.69%) (Fig. 4). A low adherence rate is closely related to DRPs, an important determinant of non-adherence. We identified 230 DRP-related events and the number of patients showing non-adherence was 453 and 513 at the 6- and 12-month follow-up, respectively. Approximately 50% of cases of non-adherence to drugs were attributable to wrong drug administration.

Statistical analysis performed using the Student’s t-test showed a significant difference in the adherence rates reported by patients at the 6- and 12-month follow-up time points (P < 0.001).

The MANOVA showed a statistically significant overall difference in adherent and non-adherent patients (P < 0.011), which was caused by the score of DRPs.

**DISCUSSION**

BPH represents a major public health issue because of its high prevalence, progressive nature, and associated economic costs (19). Current guidelines recommend the use of AB and 5ARI alone or in combination for the treatment of LUTS/BPH (20). High adherence to prescribed medications is very important for the management of chronic diseases (14). To date, limited information is available regarding clinical outcomes in terms of drug prescriptions, patient adherence, and the influence of pharmacological treatment of LUTS/BPH (21).
Our study results demonstrate that adherence to pharmacological therapy for the treatment of BPH was low, and the 12-month drug adherence rate was observed to be 23%. We observed a significant relationship between drug adherence rates and the duration of treatment - longer duration of pharmacological therapy is associated with a lower drug adherence rate. The same relationship between the number of adherent patients and groups of drugs was observed over 2 periods of follow-up. There is a distinct relationship between adherence rate and the degree of LUTS/BPH - the higher degree of LUTS/BPH, the higher adherence rate. The therapy discontinuation rate was observed to be 11.61%.

Furthermore, our study shows that a low adherence rate is closely related to DRPs (Fig. 4). It should be highlighted that the top categories of DRPs were drug problems (37.39%), drug use process (23.04%), adverse reactions (20.86%), and drug choice problems (18.69%). Among these categories of DRPs, the most often problems related to drugs were drug dose too low or dosage regimen not frequent, duration of treatment too short and inappropriate timing of administration, and inappropriate drug.

Low adherence results in poor health outcomes, a lower quality of life, and increased health care costs. Adherence is related to perceived efficacy, adverse effects, and economic costs of treatment. Previous reports have demonstrated that
patients with worse LUTS complain lesser regarding adverse effects than those with less severe symptoms (22). Notably, elderly men are more likely to be adherent to their medication regimen. Our study demonstrated that 75.76% of patients ≥ 66 years of age were adherent to drugs after administration of 12-month pharmacological therapy.

Cindolo et al. (12) report that in patients newly diagnosed with LUTS/BPH, marginal difference was observed, mean adherence rates between different groups of drugs were 67% AB, 73% SARI, 71% CT. In turn, Nichol et al. (23) report that in a study population comprising 2640 men, the adherence rate for any LUTS/BPH medication was 40%.

In patients diagnosed with LUTS/BPH, adherence to pharmacotherapy is closely related to the patient’s discomfort level associated with intake of the medication, and to patient expectations (24). BPH is not a life-threatening disease entity but is potentially progressive. It should be highlighted that the patient plays a key role in deciding to initiate and/or continue treatment (25).

Recently, medication regimens have been simplified via use of extended-release formulations and/or fixed-dose combination pills. Additionally, memory aids and/or reminders are made available to patients. These are a few of the interventions that have been developed to improve adherence (26).

The results of this study showed a low adherence rate and the need of simplifying polypharmacy. Therefore, in the future, adherence rate would be hopefully higher. Further studies will be conducted to assess if the new interventions and simplifications are efficient.

Conclusions

Our study shows a low rate of overall drug adherence in patients diagnosed with BPH. It was observed that a low adherence rate is closely related to drug-related problems (DRP). Furthermore, this is a correlation between the degree of LUTS/BPH and adherence rate - the higher degree of LUTS/BPH, the higher adherence rate. Further studies are warranted focusing on assessing adherence to pharmacological therapy.

Authors’ contribution: T.Z. conceived the idea for the study. T.Z. and M.S. contributed to the design of the research. T.Z. was involved in data collection and analyzed the data. Both authors edited and approved the final version of the manuscript.

Conflict of interests: None declared.

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