Pharmacotherapy of patients with benign prostate enlargement and storage symptoms in daily clinical practice

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Abstract

Purpose: Storage symptoms significantly deteriorate the quality of life in men with benign prostate enlargement (BPE). Muscarinic receptor antagonists (MRAs) and β3-adrenergic receptors agonists alone, or in combination with selective α1-alpha-antagonists (ARAs), are considered as the most effective medicines relieving storage symptoms. The aim of this study was to analyze pharmacotherapy of storage symptoms in men with BPE, and their compliance with the European Association of Urology (EAU) guidelines. Patients and methods: The survey was conducted in 2018 by 261 urologists among 37,165 outpatients with lower urinary tract symptoms (LUTS) treated pharmacologically, including 24,613 men with BPE (age 69 ± 8 years). Data concerning recent severity of non-neurological LUTS and storage symptoms (urinary urgency, frequency and nocturia) and pharmacotherapy were collected. Results: Storage symptoms were reported by 12,356 patients (50.2%) with BPE, more frequently nocturia (75.8%), than urinary urgency (57.8%) and urinary frequency (44.3%). Patients with storage symptoms were more frequently prescribed with MRAs and mirabegron (43.1% vs. 5.0%; $p < 0.001$; and 2.4% vs 0.3%; $p < 0.001$; respectively). Of note, 54.5% of patients with storage symptoms were treated neither with MRAs nor β3-adrenergic receptors agonists. In the subgroup with storage symptoms, the increasing severity of LUTS accounted for more frequent prescription of MRA based pharmacotherapy (2.1% vs 29.1% vs 42.8% in patients with mild, moderate, and severe LUTS, respectively). Decision tree analysis revealed that patients with urinary urgency and urinary frequency as well as younger ones with urinary urgency but without urinary frequency were more frequently prescribed with MRAs. Conclusion: Urinary urgency and frequency are associated with increased utilization of MRAs in men with BPE in daily clinical practice. The attitude of Polish urologists toward management of persistent storage symptoms in BPE patients is in line with the EAU guidelines.

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Short running title: Storage symptoms pharmacotherapy in BPE

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Consultations: prof Andrzej Prajsner – retired Head and Chair of the Department of Urology, Medical University of Silesia in Katowice.

Ethics: according to the Polish law, surveys are not medical experiments and as such do not require either Bioethical Committee approval or the need to obtain informed consent from the patients for inclusion.

Disclosure

Romuald Zdrojowy received a consultation fee for the manuscript editing. Aleksander Jerzy Owczarek received honorarium for statistical analysis. Magdalena Olszanecka-Glinianowicz received honorarium for the project drafting. Agnieszka Almgren-Rachtan is employed by Europharma Rachtan Co. Ltd (Director of the Department of Pharmacovigilance). Jerzy Chudek received honorarium for data analysis and manuscript drafting.

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Abstract

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The aim of this study was to analyze pharmacotherapy of storage symptoms in men with BPE, and their compliance with the European Association of Urology (EAU) guidelines.

Patients and methods: The survey was conducted in 2018 by 261 urologists among 37,165 outpatients with lower urinary tract symptoms (LUTS) treated pharmacologically, including 24,613 men with BPE (age 69 ± 8 years). Data concerning recent severity of non-neurological LUTS and storage symptoms (urinary urgency, frequency and nocturia) and pharmacotherapy were collected.

Results: Storage symptoms were reported by 12,356 patients (50.2%) with BPE, more frequently nocturia (75.8%), than urinary urgency (57.8%) and urinary frequency (44.3%). Patients with storage symptoms were more frequently prescribed with MRAs and mirabegron (43.1% vs. 5.0%; $p < 0.001$; and 2.4% vs 0.3%; $p < 0.001$; respectively). Of note, 54.5% of patients with storage symptoms were treated neither with MRAs nor β_3-adrenergic receptors agonists. In the subgroup with storage symptoms, the increasing severity of LUTS accounted for more frequent prescription of MRA based pharmacotherapy (2.1% vs 29.1% vs 42.8% in patients with mild, moderate, and severe LUTS, respectively).

Decision tree analysis revealed that patients with urinary urgency and urinary frequency as well as younger ones with urinary urgency but without urinary frequency were more frequently prescribed with MRAs.

Conclusion: Urinary urgency and frequency are associated with increased utilization of MRAs in men with BPE in daily clinical practice. The attitude of Polish urologists toward management of persistent storage symptoms in BPE patients is in line with the EAU guidelines.

Kew words: non-neurogenic Lower Urinary Tract Symptoms, pharmacotherapy, real-life data, muscarinic receptor antagonists, urinary urgency, urinary incontinence

WHAT'S KNOWN?

Till now the only knowledge concerning the daily prescribing practice of Polish urologists in men with lower urinary tract symptoms (LUTS) is coming from a survey performed, shortly after the publication of the 2013 edition of the European Association of Urology (EAU) guidelines. This survey assessed the urologists declarations concerning therapy, but did not verify their daily prescribing practice.

WHAT'S NEW?

We present for the first time real-life data concerning current pharmacotherapy for benign prostate enlargement (BPE) and the effect of storage symptoms on the utilization of urological drugs, including muscarinic receptor antagonists in Poland. We showed the attitude of Polish urologists toward management of persistent storage symptoms in BPE patients in line with the EAU guidelines. Currently, muscarinic receptor antagonists are more frequent used in triple, than double schedule, probably due to relatively high costs of these drugs.

Introduction

Extension of the lifetime in developed countries results in the increase in the prevalence of benign prostatic hyperplasia (BPH) and related, so called non-neurogenic lower urinary tract symptoms (LUTS) [1]. Progressive prostate enlarging impairs the outflow of urine from the bladder, known as bladder outlet obstruction (BOO), followed by hypertrophy and overactivity of the detrusor muscle [2]. BOO impairs both emptying and storage of urine in the bladder, that are manifested by weakness of the urine stream, incomplete emptying, frequent urination, urgency, and nocturia, in the absence of urinary tract infection and other urethro-vesical dysfunctions. The occurrence of symptoms deteriorate, to a various extend, the quality of life including sleep disorders, anxiety, embarrassment associated with the disease, reduced mobility, as well as impairment of sexual activity and satisfaction with sexual relations [3, 4, 5, 6].

The majority of men with non-neurogenic LUTS can be treated conservatively. The European Association of Urology (EAU) in 2000 developed guidelines (and updated them in 2019) on the management of non-neurogenic male LUTS including publications from 2017 [7]. According to these guidelines, pharmacotherapy in BPH should not be offered to men with mild/moderate LUTS, minimally bothered by their symptoms (watchful waiting). While the therapy (monotherapy) with selective α1-alpha- antagonists (ARAs) should be initiated in those with moderate-to-severe symptoms. ARAs are effective in reducing LUTS and increasing

the peak urinary flow rate, but neither reduce prostate volume, nor prevent acute urinary retention (AUR). 5-α reductase inhibitors (5αRIs) should be offered in monotherapy or in combination with ARAs, to men with moderate-to-severe symptoms and an increased risk of disease progression (prostate volume > 40 mL). These drugs have delayed onset of action and may reduce libido, deteriorate potency and cause ejaculation disorders, but increase the peak urinary flow rate, decrease prostate volume and the risk of AUR as well as the need for surgery. In addition, in men with bladder storage symptoms, but without increased void residual volume (> 150 mL), the guidelines recommend the use of muscarinic receptor antagonists (MRAs). These drugs can significantly improve urgency, urinary incontinence, and increased daytime frequency. Finally, the guidelines recommend the use of tadalafil as the only phosphodiesterase 5 (PDE5) inhibitor with some potency to improve LUTS and urinary flow rate, and β_3-adrenoceptors agonist (mirabegron) in men with moderate-to-severe LUTS who have mainly bladder storage symptoms, as an alternative of MRAs due to better patients adherence.

Pharmacotherapy for non-neurogenic LUTS, should be individualized taking into account not only the severity and structure but also dominance of certain symptoms, as well as prostate volume, co-morbidities and patient expectations and preferences. In patients with mostly storage LUTS, the first-line treatment should be lifestyle advice and behavioural modifications (restriction of caffeine, alcohol and fluid intake at the evening, weight reduction in overweight and obese, training of bladder control strategies) [8]. If not effective, MRAs and β_3-adrenoceptors agonists, alone or in combination with ARAs [9, 10, 11] are more effective than other pharmacological strategies. While in men with concomitant voiding LUTS in course of BPO, ARAs and 5αRIs allow the improvement in the storage symptoms [12].

A survey performed among Polish urologists, shortly after the publication of the 2013 edition of EAU guidelines, showed that 10% urologists start pharmacotherapy in patients with minimal-to-moderate LUTS. ARAs were the first line treatment option both for patients with (48.8% urologists) and without (84.8% urologists) benign prostate enlargement (BPE) while only 17.1% urologists were choosing 5αRIs in monotherapy, and 29.6% prescribed them with ARAs as the primary treatment. MRAs were an acceptable treatment option for storage LUTS in the opinion of 83.7% of urologists [13]. This survey assessed the urologists declarations concerning therapy, but did not verify their daily prescribing practice.

The aim of this study was to to analyze pharmacotherapy of storage symptoms in men with BPE, and their compliance with guidelines.

Patients and methods

This large cohort study was carried out in 2018 by 231 urologists and 30 under-training residents, on a group of 37,165 outpatients (men) with LUTS, pharmacologically treated for at least two weeks. Patients agreement to participate in the survey was the only additional inclusion criteria for eligible outpatients. Inability to obtain answers to questions in the questionnaire was the only exclusion criterion. The survey did not meet the criterion of a medical experiment and did not require an approval of the Bioethical Committee. The study organizer (Europharma Rachtan Co. Ltd.) processed only anonymized patients' data.

Survey procedures

Urologists were recruited among doctors working in urological outpatient clinics, effectively collaborating in the previous projects. The survey was supported by a study questionnaire, that was filled out by the investigator, participating in the survey based on an interview and data from the medical history during a single visit resulting from clinical needs. Data of eligible patients that refused to participate were not collected.

The individual patients' questionnaire included data concerning: age, educational level, place of residence, clinical data (period of time since the diagnosis of BPH, the occurrence of enlarged prostate volume (> 30 mL in transabdominal sonography), storage symptoms (nocturia, urinary frequency, urinary urgency, and urge incontinence), recent severity of LUTS according to the International Prostate Symptom Score (I-PSS)

reported as mild (0-7 pts), moderate (8-19 pts) and severe (20-35 pts) [14], current pharmacotherapy for BPH, and main factors that affected the drugs choice.

The survey was combined with patients' education concerning methods of involuntary urination management if needed.

Statistical analysis

There were 37,165 questionnaires completed by the investigators. Patients records without prostate enlargement (< 30 ml in transabdominal sonography examination) and those with missing data were excluded (N = 12,552). Statistical analysis was performed using the STATISTICA 13.0 PL software (Tibco Software Inc, Palo Albo, USA), StataSE 12.0 (StataCorp LP, TX, U.S.). Statistical significance was set at a p -value below 0.05. All tests were two-tailed. No data imputation was performed. Nominal and ordinal data were expressed as percentages, while interval data were expressed as mean value ± standard deviation. Distribution of variables was evaluated by the Shapiro-Wilk test and the Cullen-Frey graph. Homogeneity of variances was assessed by the Fisher-Snedecor test. For comparison of data, the one-way ANOVA analysis was used with RIR Tukey posthoc test. Categorical variables were compared using χ^2 tests. Classification and regression trees were built with Gini index as a measure of goodness of fit, equal classification error and 10-times cross validation.

Results

Study group characteristics

The analysis included 24,613 of 37,165 men prescribed with medication for BPH at the mean age of 69 ± 8 yrs., currently reporting mild (23.1%), moderate (67.5%) or severe (9.4%) LUTS. Storage symptoms were reported by 12,356 patients (50.2%), most frequently nocturia – 75.8%, than urinary urgency (usually without urine incontinence) – 57.8%, and urinary frequency – 44.3%. Patients with storage symptoms were characterized by higher prevalence of men with severe LUTS and those with over 5 yrs. history of treatment for BPH (Tab. 1).

BPH pharmacotherapy

In the entire study group, the most commonly used pharmacotherapy was ARAs in monotherapy – 36.6%, or in a combination therapy with 5αRIs – 30.9%. MRAs were prescribed either with ARAs – 11.2%, or on top of ARA+5αRI therapy – 30.9%. Mirabegron, the only available in Poland selective β_3-adrenoceptors agonist, was used in 1.4% of men only (Tab. 1).

Patients with storage symptoms were more frequently prescribed with MRA containing pharmacotherapy and/or mirabegron (43.1% vs. 5.0%; $p < 0.001$; and 2.4% vs 0.3%; $p < 0.001$; respectively). Of note, 54.5% of patients with storage symptoms were not treated with MRAs and/or β_3-adrenergic receptors agonists.

In the subgroup of patients with storage symptoms increasing severity of LUTS accounted for more frequent prescription of MRA-based pharmacotherapy (from 2.1% in patients with mild, through 29.1% with moderate, to 42.8% with severe LUTS). In patients with moderate LUTS MRAs were used with similar frequency with ARAs and with ARA+5αRI; while in individuals with severe LUTS much more frequently on top of ARA+5αRI therapy (Tab. 2).

Tamsulosin was the most commonly used ARA (70.1%), while doxazosin (20.0%) and alfuzosin (6.2%) came second and third. With the increasing severity of LUTS, the prescription of doxazosin within ARAs was increasing (from 16.9 to 24.4%, $p < 0.001$), while the prescription of alfuzosin was decreasing (from 5.8 to 3.3%; $p < 0.001$). The occurrence of urinary urgency was associated with more frequent use of doxazosin (14.0 vs 22.4%; $p < 0.001$) but less frequent use of tamsulosin (75.1 vs 68.0%; $p < 0.001$) and alfuzosin (7.5 vs 5.7%; $p < 0.001$). The data concerning the use of specific 5αRIs was not collected, as finasteride is the almost exclusively used 5αRI in Poland.

Of the available MRAs, tolterodine (20.2%) and solifenacin (9.0%) were most commonly used; while oxybutynin (1.4%), and darifenacin (0.1%) were used much less frequently.

Decision trees

Patients with moderate/severe severity of LUTS, older and with higher educational level (73.1%) were more likely to be prescribed with 5αRIs – Fig. 1.

Similarly, patients with urinary urgency with urinary frequency (72.4% of them) as well as younger ones with urinary urgency but without urinary frequency (74.8% of them) were more likely to receive prescription for MRAs – Fig 2.

Discussion

Our real-life data concerning current pharmacotherapy for benign prostate enlargement (BPE) shows that ARAs monotherapy remains as the most frequent therapeutic option utilized in more than one-third of patients. It is in line with the survey performed among Polish urologists, showing that ARAs in monotherapy was the first line option for patients with and even without BPE [13]. When comparing the prescribed medication for non-neurogenic LUTS with the data coming from PolSenior study [15], performed in years 2007 – 2012, one may see that the prescription of ARAs in monotherapy has declined from 64.7 to 25.6%, during last years, possibly as a consequence of later guidelines from 2010. In parallel, during this period of time there was an increase in the utilisation of ARA+5αRI combined therapy from 21.9% to 30.9% and most spectacularly the use of MRAs (in the combined therapy) from 1.7 to 23.6%. The increase in the utilization of MRAs, revealed by our observation, is in line with the treatment option accepted by 83.7% of Polish urologists concerning MRAs use for the management of storage LUTS [13]. While the most recently introduced drug – mirabegron is currently rarely used (1.4% of overall study population and 2.4% of those with storage symptoms), probably due to the lack of reimbursement from Polish National Health Fund. Of note, as much as 54.5% of patients with storage symptoms were treated neither with MRAs nor with β_3-adrenergic receptors agonists, despite the EAU recommendations.

Similarly to Poland, the ARAs monotherapy is the most frequently utilized medication for BOO in the USA, yet slowly decreasing during the last decade from 74.6% in 2006 to 68.7% in 2014 in favour of monotherapy with 5αRI [16]. BOO medication in the USA was characterized by more profound, than in Poland (based on our data), underutilization of MRAs. Only 3.7% of the USA cohort with BPH/LUTS were prescribed with MRAs (5.7% of those receiving other BOO medication) with no significant increase in the study period (2006-2014).

A different landscape is presented by a recent MERCURE study from Spain [17], that analysed the compliance with the EAU 2013 recommendations in the management of LUTS in men. In this study, treatment with ARAs in monotherapy and ARAs with MRAs was almost equally frequent (37.5 vs 37.2%, respectively).

Having in mind the recommended individualization of pharmacotherapy for non-neurogenic LUTS, that take into account not only the severity, prostate volume, structure / dominance of certain symptoms, but also co-morbidities as well as patients' expectations and preferences, we analysed how storage symptoms (urinary urgency, frequency and nocturia) affects the prescription of 5αRI and MRAs. We have demonstrated that decisions concerning pharmacotherapy with MRAs was affected mostly by the occurrence of urinary urgency and urinary frequency, but not nocturia, among the storage symptoms. In addition MRAs were more frequently prescribed in younger adults (< 65 years old). While the decision concerning the use of 5αRI was mostly affected by severity of LUTS, older age and education level.

The more frequent choice of 5αRI in older men is potentially explainable by a benefit from reducing the risk of prostate cancer during long-term with these drugs [18], while bearing the risk of decrease in libido, ejaculation disorders and painful enlargement of the breast [19]. However, it is hard to say whether it reflects patients' preferences or the knowledge of the physicians.

The relatively high costs of MRAs therapy in Poland probably explain the more frequent use of these drugs

in triple, rather than double schedule, and more prevalent utilization of cheaper tolterodine rather than solifenacin (in 20.2 and 9.0% of MRAs users, respectively). In line with this statement is the low utilization of mirabegron (more expensive than MRAs), the only currently available β_3-adrenoceptors agonist, in patients with storage symptoms. Our data indirectly demonstrates how per capita income modifies the application of the EAU recommendations in European societies.

Study limitations are related to the methodology. The survey was focused mostly of the current clinical presentation of storage symptoms, and not those preceding the initiation of pharmacotherapy. The survey did not collect the data concerning the changes in medication during the therapy. We cannot exclude some overrepresentation of patients with more severe symptoms, potentially, more frequently utilizing medical services. The generalization of the data is restricted to Polish population due to the effect of drug reimbursement policy by the national health system.

In conclusion: urinary urgency and frequency are associated with increased utilization of MRAs in men with BPE in daily clinical practice. The attitude of Polish urologists toward management of persistent storage symptoms in BPE patients is in line with EAU guidelines.

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Table 1: The characteristics of the analysed group of men with prostatic enlargement, pharmacologically treated for BPH.

	Whole group	**Storage symptoms**	**Storage symptoms**	**p**
		YES	**NO**	
	[N=24,613]	[N=12,356]	[N=12,257]	
Age [years]	69 ± 8	70 ± 9	68 ± 8	<0.001
Age [?] 65 yrs. [N; %]	17,404; 70.7	9,281; 75.1	8,123; 66.3	<0.001
Education level [N; %]				
Primary	2,391; 9.7	1,314; 10.6	1,077; 8.8	<0.001
Vocational	6,499; 26.4	4,165; 33.7	2,334; 19.0	
Secondary	11,192; 45.5	4,637; 37.5	6,555; 53.5	
Higher	4,531; 18.4	2,240; 18.1	2,291; 18.7	
Place of residence [N; %]				
Rural	4,667; 19.0	2,764; 22.4	1,903; 15.5	<0.001
Small city (< 50 ths. inhabitants)	5,666; 23.0	2,665; 21.6	3,001; 24.5	
Large city ([?]50 ths. inhabitants)	14,280; 58.0	6,927; 56.0	7,353; 60.0	
Period of time since the diagnosis of BPH [N; %]				
[?] 5 yrs.	16,407; 66.7	7,805; 63.2	8,602; 70.2	<0.001
> 5 yrs.	8,206; 33.3	4,551; 36.8	3,655; 29.8	
Severity of LUTS [N; %]				
0-7 pts – mild	5,681; 23.1	986; 8.0	4,695; 38.3	<0.001
8-19 pts – moderate	16,608; 67.5	9,495; 76.8	7,113; 58.0	

	Whole group	**Storage symptoms**	**Storage symptoms**	**p**
20-35 pts – sever	2,324; 9.4	1,875; 15.2	449; 3.7	
Storage symptoms				
Urinary urgency [N; %]	7,139; 29.0	7,139; 57.8	-	-
without incontinence	6,359; 25.8	6,359; 51.5	-	-
with incontinence	780; 3.2	780; 6.3	-	-
Nocturia [N; %]	9,369; 38.1	9,369; 75.8	-	-
Urinary frequency [N; %]	5,470; 22.2	5,470; 44.3	-	-
Medication for BPH [N; %]				
Phytotherapy	263; 1.1	195; 1.6	68; 0.6	<0.001
ARA	8,997; 36.6	2,093; 16.9	6,904; 56.3	<0.001
5αRI	1,477; 6.0	662; 5.4	815; 6.7	<0.001
ARA + MRA	2,749; 11.2	2,356; 19.1	393; 3.2	<0.001
ARA + 5αRI	7,596; 30.9	3,781; 30.6	3,815; 31.1	<0.001
ARA + 5αRI + MRA	3,191; 13.0	2,965; 24.0	226; 1.8	<0.001
ARA + 5αRI + MIR	323; 1.3	288; 2.3	35; 0.3	<0.001
ARA + 5αRI + MRA + MIR	17; 0.1	16; 0.1	1; 0.01	-

ARA - selective α1-alpha-adrenolytic

5αRI - 5-alpha reductase inhibitor

MIR - mirabegron

MRA - muscarinic receptor antagonist

Table 2: Comparison of patients with prostatic enlargement and storage symptoms in respect to the severity of LUTS.

	Severity of LUTS	**Severity of LUTS**	**Severity of LUTS**	**p**
	[?] 7 pts. [N=5,681]	**8-19 pts.** [N=16,608]	**[?] 20 pts.** [N=2,324]	
Age [years]	68 ± 8	69 ± 8	72 ± 7	<0.001
Age [?] 65 yrs. [N; %]	3,794; 66.8	11,602; 69.9	2,008; 86.4	<0.001
Period of time since the diagnosis of BPH [N; %]				
[?] 5 yrs.	3,913; 68.9	11,549; 69.5	945; 40.7	<0.001
> 5 yrs.	1,768; 31.1	5,059; 30.5	1,379; 59.3	

	Severity of LUTS	**Severity of LUTS**	**Severity of LUTS**	**p**
Urinary urgency [N; %]	189; 3.3	5,775; 34.8	1,175; 50.6	<0.001
without incontinence	189; 3.3	5,055; 30.4	1,115; 48.0	<0.001
with incontinence	0	720; 4.3	60; 2.6	
Nocturia [N; %]	887; 15.6	6,765; 40.7	1,717; 73.9	<0.001
Urinary frequency [N; %]	135; 2.4	4,452; 26.8	883; 38.0	<0.001
Medication for BPH [N; %]				
Phytotherapy	74; 1.3	189; 1.1	0	<0.001
ARA	4,270; 75.2	4,570; 27.5	157; 6.8	<0.001
5αRI	182; 3.2	1167; 7.0	128; 5.5	<0.001
ARA + MRA	91; 1.6	2,410; 14.5	248; 10.7	<0.001
ARA + 5αRI	364; 14.4	3,118; 31.5	858; 43.8	<0.001
ARA + 5αRI + MRA	31; 0.6	2,414; 14.6	746; 32.1	<0.001
ARA + 5αRI + MIR	144; 2.5	176; 1.1	3; 0.1	<0.001
ARA + 5αRI + MRA + MIR	0	16; 0.1	1; 0.04	<0.001

ARA - selective α1-alpha-adrenolytic

5αRI - 5-alpha reductase inhibitor

MIR - mirabegron

MRA - muscarinic receptor antagonist

Legends to the figures:

Figure 1: Decision tree for the use of 5αRI - 5-alpha reductase inhibitor in the study group. Accuracy of this decision tree was 70.1%.

Figure 2: Decision tree for the use of MRA - muscarinic receptor antagonist in the study group. Accuracy of this decision tree was 83.5%.