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ORIGINAL RESEARCH

The Risk of Sexual Dysfunction and Effectiveness of Treatment of Benign Prostatic Hyperplasia With Severe Lower Urinary Tract Dysfunction With Combination of Dutasteride and Solifenacin

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ABSTRACT

Introduction: Correction of benign prostatic hyperplasia (BPH) with lower urinary tract (LUT) symptoms (LUTS) is treated with drugs of different pharmacological classes having side effects including suppression of sexual function.

Aim: To assess the effect of simultaneous intake of dutasteride and solifenacin on the reversibility of severe LUTS and sexual function in men with BPH.

Methods: Patients from group A took dutasteride 0.5 mg/d, those from group B took dutasteride 0.5 mg/d and solifenacin 10 mg/d, and those from group C took dutasteride 0.5 mg/d and solifenacin 20 mg/d. The duration of the observation was 6 months. The sexual function was rated with the International Index of Erectile Function questionnaire and Men's Sexual Health Questionnaire—ejaculatory dysfunction. The functional status of LUT was rated with International Prostate Symptom Score, overactive bladder questionnaire—awareness tool, diary voiding, and uroflowmetry.

Main Outcome Measure: The state of sexual function and function of the LUT in men improved.

Results: The erectile function in all men, having participated in the study, did not change [group A, 9.8 (1.6)/9.4 (3.8), $P \geq .05$; group B, 10.1 (2.1)/10.5 (3.7), $P \geq .05$; group C, 9.7 (1.5)/9.5 (2.6), $P \geq .05$]. The ejaculator function significantly decreased in all groups. According to International Prostate Symptom Score, obstruction diminished in this group [incomplete emptying, 3.7 (0.7)/1.5 (0.3), $P \leq .05$; intermittence, 3.5 (1.0)/3.5 (1.0), $P \leq .05$; weak stream, 3.8 (0.6)/1.5 (0.4), $P \leq .05$; straining, 3.4 (0.5)/0.7 (0.7), $P \leq .05$] as did hyperactivity [urgency, 2.8 (0.7)/0.9 (0.7), $P \leq .05$; nocturia, 2.8 (0.6)/1.2 (0.4), $P \leq .05$]. All numbers in the manuscript are given in points unless otherwise stated. The values in parentheses are SD (unless otherwise specified).

Clinical Implications: The information that a high dose of solifenacin administered concomitantly with dutasteride may contribute to increase in sexual satisfaction and preservation of erectile function at the baseline level can be useful and used by sexologists, urologists, and family doctors.

Strength & Limitations: The combination of dutasteride 0.5 mg/d and solifenacin 10 mg/d saves erectile function and improves sexual satisfaction. At the same time, the symptoms of obstruction and hyperactivity disappear or are reduced in most patients. Nevertheless, we did not study late results of the combined therapy.

Conclusion: Suggested combination does not impact on erectile function but decreases ejaculator function; however, it does not affect a general high rating of sexual function by patients. Thus, overall sexual function in men with BPH and severe LUTS is not impaired by prolonged intake of double dosage of solifenacin combined with dutasteride. The combination of dutasteride and solifenacin is effective and safe to treat BPH and severe LUTS. **Kosilov K, Kuzina I, Kuznetsov V, et al. The Risk of Sexual Dysfunction and Effectiveness of Treatment of Benign Prostatic Hyperplasia With Severe Lower Urinary Tract Dysfunction With Combination of Dutasteride and Solifenacin. J Sex Med 2018;15:1579–1590.**

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Key Words: Sexual Dysfunction; Benign Prostatic Hyperplasia; Lower Urinary Tract Symptoms; Dutasteride; Solifenacin

INTRODUCTION

Prevalence of benign prostatic hyperplasia (BPH) is very high and is from 50−75% among men age 50 years and older, to 80% among men age 70 years and older. Many millions of middle-aged men and elderly men are subject to BPH in national populations. For example, in the United States, over 15 million men have diagnosis of BPH.[1,2] The risk of developing BPH in the future for a 46-year-old man during 30 years is not less than 45%.[3]

The occurrence of BPH is associated with several factors. One of the mechanisms of development of BPH is to increase the level of lipids in the blood. Hypogonadism and/or hyperestrogenism, a chronic inflammation of a prostate gland related to the infection, also has great significance to pathogenesis of BPH. At least 2 of 3 listed factors are able to cause the decrease of oxygenation of a prostate gland, persistent spasms of unstriated muscle, and afferent innervations disorders. As a result, there is an unregulated proliferation of the connective tissue, unstriated muscle, and glandular epithelium in the prostate gland.[4−6]

BPH often shows as a complex of pathological lower urinary tract (LUT) symptoms (LUTS), including not only weak stream, straining, incomplete emptying, that would be natural, but also sexual dysfunction, nocturia, urgency, and increase of daytime and nighttime frequency of urination. These symptoms can be possibly explained by some common mechanisms of both BPH and LUTS. In recent decades it was found that in the pathogenesis of BPH and LUTS the atherosclerosis of pelvic organs, autonomic adrenergic hyperactivity, alteration of the nitric oxide-cyclic guanosine monophosphate pathway, enhancement of RhoA-Rho-kinase contractile signaling, and some other manifestations of metabolic syndrome are essential.[7,8]

The nocturia, increase of nighttime frequency, urge urinary incontinence and sexual dysfunction may lead to psychoemotional instability, depression, a decrease quality of life related to health.[3,8]

Drug-induced correction of BPH with LUTS includes the use of several ranges of medications, each of them has advantages but still has some disadvantages. Phosphodiesterase type-5 inhibitors and anti-muscarinic drugs were relatively recently added to long used α1-adrenergic blockers and 5α-reductase inhibitors.[9−11] Currently, medicines from different pharmacological groups are used to treat BPH. Such an approach sometimes enables to supplement and to strengthen a clinical effect using different mechanisms of action on the target organ in respect of individual susceptibility to drugs. For example, we have studied safety and effectiveness of simultaneous intake of tamsulosin and solifenacin,[12−14] tamsulosin and dutasteride,[15] dutasteride and tadalafil, etc. Nevertheless, many questions related to drug combination, of different classes in therapy of LUTS remain open.[16]

Well-known 5α-reductase type 1 and 2 inhibitor dutasteride reduces concentration of 5α-dihydrotestosterone. The effectiveness of this medicine in reducing the volume of enlarged prostate gland is considered to be proven. It reduces the risk of acute urinary retention and the probability of surgical treatment as well, and it increases the quality of life and treatment satisfaction.[16,17] However, many researchers claim that prostate volume reduction after taking dutasteride is not always accompanied by reversibility of LUTS.[18] Moreover, there are data on negative effects of this 5α-reductase inhibitor on libido, erectile and ejaculator functions, and semen quality.[19]

Solifenacin is a selective competitive M-cholinoreceptors inhibitor prevalently of M_3-type, which effectively blocks the effect of acetylcholine and relaxes detrusor muscle. It leads to the improvement of local micro-circulation and the increase of tissue oxygenation.[20,21] The literature has data both on solifenacin effectiveness in erectile dysfunction[22] and the opposite study results.[23] In earlier studies we found that solifenacin of elevated dosage is safe and produces a good clinical effect in administration to patients with BPH and LUTS.[12,13] There are also data that pathogenesis of erectile dysfunction and LUTS may have some common mechanisms.[24] Nowadays there are only isolated and contradictory reports on successful use of the combination 5α-reductase and anti-muscarinic drugs in BPH with LUTS.[25] However, the question is how expedient this treatment algorithm may be in the correction of severe LUTS in patients with BPH, and how it can influence sexual function of patients, still remains uncovered.

Based on this understanding, we formulated the objective of our study: to evaluate effectiveness of BPH treatment with severe storage LUTS combination of dutasteride and solifenacin in a standard and increased dose, as well as to analyze changes in different aspects of sexual function of men against the background of such treatment.

METHODS

Meeting the ethical standards passed in the Declaration of Helsinki with additions passed in Seoul (in 2008) during the research was obligatory. The design of the study was approved by the local ethics committee. The written informed consents to participate in the experiment were obtained from each participant before the start of the experiment.

Table 1. Sociodemographic and physiological characteristics and parameters associated with health in men with benign prostatic hyperplasia and severe lower urinary tract symptoms (n = 317)

	Group A N = 106		Group B N = 99		Group C N = 112	
Parameters	Mean or N	(SD) or %	Mean or N	(SD) or %	Mean or N	(SD) or %
Age, y	57.9	(8.1)	61.5	(11.8)	61.9	(13.7)
Married	67	63.2	77	77.7	81	72.3
Unmarried	39	36.8	22	22.2	29	25.9
Professionally active	56	52.8	42	42.4	49	43.7
Full working day	21	37.5	14	33.3	10	20.4
Undertime	22	39.3	20	47.6	35	71.4
Combining work	13	23.3	6	14.3	2	4.1
Receive a pension	50	47.2	57	57.6	63	56.2
Rural areas	36	33.9	23	23.2	41	36.6
City areas	70	66.1	76	76.8	71	63.4
Education						
Secondary	31	29.2	19	19.1	25	22.3
Vocational	33	31.1	29	29.3	43	38.4
Higher	42	39.6	51	51.5	44	39.3
Normal weight	89	83.9	88	88.8	94	83.9
Overweight*	17	16.1	11	11.2	18	16.1
I-PSS, score sum	24.2	(5.8)	26.5	(7.3)	26.7	(5.1)
OABq-AT, score sum	56.2	(16.3)	45.4	(10.4)	49.1	(16.6)
Level of PSA ng/mL	3.8	(1.6)	4.1	(0.9)	5.0	(2.1)
Uroflowmetry						
PVR, mL	37.5	13.6	51.5	10.9	44.8	16.9
Q_{aver}, mL/s	9.4	3.0	10.4	2.8	10.8	3.8
Q_{max}, mL/s	14.7	4.8	12.8	4.9	14.8	4.6
Diary of voiding						
Daytime frequency	9.9	1.7	7.9	0.8	9.1	2.4
Nighttime frequency	3.4	1.2	2.8	1.3	2.7	0.8
Urgency	1.6	0.7	1.5	0.6	1.2	0.2
Incontinence episodes	0.6	0.2	0.5	0.5	0.4	0.3
Prostate volume, mL	39.6	5.8	36.9	7.1	40.5	4.3
MSHQ-EjD, score sum	63.6	4.7	60.7	5.2	62.0	4.8
IIEF, score sum	47.4	6.8	48.5	5.7	47.0	4.2

I-PSS = International Prostate Symptom Score; OABq-AT = overactive bladder questionnaire—awareness tool; PSA = prostatic-specific antigen; MSHQ-EjD = Men's Sexual Health Questionnaire—ejaculatory dysfunction; IIEF = International Index of Erectile Function; PVR = post-void residual urine volume; Q_{aver} = average flow rate; Q_{max} = maximum flow rate.
*According to the World Health Organization recommendation the overweight patients were $\geq$25 kg/m^2.

The random research was done at Far Eastern Federal University and City Outpatient Clinic No. 3, Vladivostok, from June 1, 2016, to January 15, 2017. It included patients with the first established diagnosis: BPH. Entry criteria were severe LUTS (score 20 and over on the International Prostate Symptom Score [I-PSS])[26] and age 50 years and older. According to the examination record, 317 patients were divided into 3 groups randomly. Group A included patients who were prescribed dutasteride 0.5 mg/d; group B included patients who were prescribed dutasteride 0.5 mg/d and solifenacin 10 mg/d; and group C included patients who were prescribed dutasteride 0.5 mg/d and double dosage of solifenacin: 20 mg/d. A planned period of treatment and observation was 6 months. Drugs were taken once in the evening. Patients did not purchase the medicines on their own, and weekly received from the operator of the research group micro-containers with tubes containing a single dose of medicines for each day of the week. Name and mechanism of action of the medicines were not known to the patients. In the process of treatment, contacts between patients were excluded (they could not exchange information). During the observation and intermediate examination, the data were depersonalized by assigning to each information case a random serial number (using a random number generator). The operator making a statistical evaluation of the obtained data had no information on the method of treatment used in each of 3 groups. Table 1 provides anthropological, social and demographical, and physiological

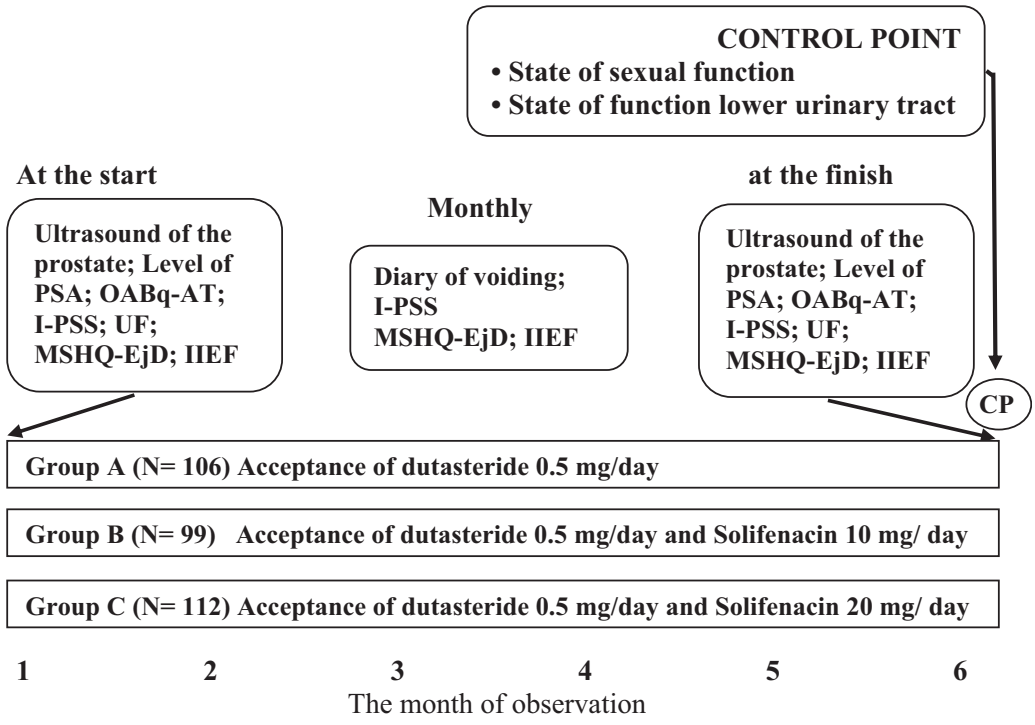

Figure 1. Study design (N = 317). IIEF = International Index of Erectile Function; I-PSS = International Prostate Symptom Score; MSHQ-EjD = Men's Sexual Health Questionnaire—ejaculatory dysfunction; OABq-AT = overactive bladder questionnaire—awareness tool; PSA = prostatic-specific antigen; UF = uroflowmetry; CP = control point.

features of the patients. There were no significant differences of the variables between groups. Figure 1 shows the study design.

Reference point of the study is evaluation of sexual function, as well as objective and subjective assessment of urodynamics of the LUT in men 6 months after initiation of combined therapy with dutasteride and solifenacin.

LUT functions at the start, further monthly, and at the end were controlled with the I-PSS questionnaire and diary voiding.[27] In addition, at the start and at the end of the research, ultrasound examination of the prostate was run and the prostatic-specific antigen was determined for all participants. The LUT functions was studied with the overactive bladder questionnaire—awareness tool (OABq-AT)[28] and uroflowmetry.[29]

Sexual function was assessed monthly with the International Index of Erectile Function (IIEF) questionnaire and Men's Sexual Health Questionnaire—ejaculatory dysfunction (MSHQ-EjD).[19,30] The commonly used questionnaire IIEF-15 is primarily oriented to the assessment of erectile dysfunction and provides an opportunity to study this aspect of sexuality accurately and thoroughly. This variant of the questionnaire that we used in this study contains 15 questions in 5 domains (erectile function, satisfaction with sexual intercourse, orgasmic function, libido, overall satisfaction) and validated in Russian.

However, it does not enable a comprehensive assessment of the sexual function, while MSHQ-EjD covers libido, orgasm function, ejaculation, and general sexual satisfaction. Regardless of partial doubling at some domains, both questionnaires complement each other well, enabling us to rate more objectively the full range of sexual functions of a particular patient.

The exclusion criteria included prostate cancer, volume of prostate gland over 45 mL, level of prostatic-specific antigen over 10 ng/mL, any chronic diseases at the long-term decompensation stage, and intake of solifenacin and/or dutasteride less than 6 months before the research.

The obtained data were processed with standard package of statistical analysis Statistics 6.0 (Dell Software Group Inc, Newport Beach, CA, USA). To compare the effects among groups we used the 1-tailed dispersion test (analyses of variance) and the Tukey-Kramer method. For the correction of type 1 errors, we applied the Bonferroni amendment. Spearman rho was used to study the correlation between the changes of variables over time. The Wald test was used as a method of verifying reliability of differences in the restriction of parameters (incomplete data due to interruption of participation in the study of part of the patient group). During the testing process, the hypothesis about reliability of differences between samples with complete and incomplete data set for all incomplete parameters was rejected. To compute the sampling frame, we assumed a 95% CI and a margin of error ±5%. Data received for statistical processing were depersonalized by assigning each case a random number. All numbers in the manuscript are given in points unless otherwise stated. The values in parentheses are SD.

A total of 41 people discontinued participation in the study (12.9%); 22 of them (6.9%) explained their decision by the

Table 2. Change in International Prostate Symptom Score, Men's Sexual Health Questionnaire—ejaculatory dysfunction, International Index of Erectile Function, overactive bladder questionnaire—awareness tool, data of voiding diaries, and uroflowmetry at the start and after treatment (n = 317)

Groups	Group A N = 106		Group B N = 99		Group C N = 112	
Observation period	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
MSHQ-EjD scores						
Overall rating	63.6 (4.7)	57.4 (4.3)	60.7 (5.2)	57.8 (5.9)	62.0 (4.8)	61.9 (6.1)
Erectile domain	9.8 (1.6)	9.4 (3.8)	10.1 (2.1)	10.5 (3.7)	9.7 (1.5)	9.5 (2.6)
Ejaculation	23.5 (2.7)	18.1 (1.7)*	22.4 (3.1)	16.8 (2.2)*	22.7 (2.6)	17.5 (1.9)*
Satisfaction	30.3 (3.6)	30.9 (2.8)	28.2 (1.6)	30.5 (2.4)	29.6 (1.8)	34.9 (2.3)*
IIEF questionnaire scores						
Overall rating	47.4 (6.8)	45.6 (4.0)	48.5 (5.7)	47.6 (2.7)	47.0 (4.2)	47.2 (6.6)
Ultrasound examination						
PV, mL	39.6 (1.8)	32.8 (1.2)*	36.9 (2.1)	31.0 (2.5)*	40.5 (2.0)	34.5 (3.1)
I-PSS questionnaire scores some parameters						
Symptoms of obstruction						
Incomplete emptying	3.5 (2.5)	1.1 (0.3)	3.7 (0.6)	1.3 (0.4)*	3.7 (0.7)	1.5 (0.4)*
Intermittence	3.7 (0.9)	0.8 (0.8)*	3.2 (0.8)	1.4 (0.9)*	3.5 (1.0)	1.2 (0.6)*
Weak stream	3.5 (0.5)	2.6 (0.8)	3.6 (0.5)	1.2 (0.6)*	3.8 (0.6)	1.5 (0.4)*
Straining	3.0 (0.9)	1.2 (0.6)*	3.6 (0.7)	1.5 (0.5)	3.4 (0.5)	0.7 (0.7)*
Symptoms of hyperactivity						
Urgency	2.7 (0.9)	1.9 (1.1)	2.6 (0.6)	1.4 (1.2)	2.8 (0.7)	0.9 (0.7)*
Nocturia	2.9 (1.2)	2.3 (0.7)	2.6 (1.7)	1.3 (0.5)	2.8 (0.6)	0.2 (0.4)*
Overactive bladder questionnaire short form scores OABq-AT some parameters						
Urgency	4.4 (1.3)	3.1 (1.3)	4.2 (1.2)	2.1 (0.6)*	4.0 (1.3)	1.2 (1.0)*
Urgency incontinence	1.0 (0.9)	0.4 (0.5)	1.3 (0.5)	0.6 (0.6)	0.9 (0.5)	0.1 (0.1)*
Nighttime frequency	3.2 (0.9)	1.7 (0.9)	3.4 (0.8)	1.4 (1.5)	3.6 (1.2)	1.2 (0.7)*
Diaries of urination, number of episodes/d						
Urgency	1.6 (0.7)	0.9 (0.9)	1.5 (0.6)	1.0 (0.6)	1.2 (0.2)	0.4 (0.4)*
Daytime frequency	9.9 (1.7)	7.4 (2.5)	7.9 (0.8)	5.6 (0.9)*	9.1 (2.4)	5.4 (0.8)*
Nighttime frequency	2.4 (1.2)	1.5 (0.4)	2.8 (1.3)	0.9 (0.3)*	2.7 (0.8)	0.9 (0.6)*
Episodes of incontinence	0.6 (0.2)	0.2 (0.3)	0.5 (0.5)	0.1 (0.2)	0.4 (0.3)	0.1 (0.1)
Urodynamic parameters, uroflowmetry						
PVR, mL	37.5 (13.6)	20.3 (10.6)	51.5 (10.9)	13.8 (9.4)*	44.8 (16.9)	14.1 (8.6)*
Q_{aver}, mL/s	9.4 (3.0)	19.7 (3.4)*	10.4 (2.8)	18.4 (2.6)*	10.8 (2.2)	17.1 (3.1)*
Q_{max}, mL/s	14.7 (4.8)	22.0 (2.1)*	12.8 (4.9)	19.4 (3.6)	14.8 (4.6)	22.8 (1.9)*

IIEF = International Index of Erectile Function; I-PSS = International Prostate Symptom Score; MSHQ-EjD = Men's Sexual Health Questionnaire—ejaculatory dysfunction; OABq-AT = overactive bladder questionnaire—awareness tool; PV = prostate volume; PVR = post-void residual urine volume; Q_{aver} = average flow rate; Q_{max} = maximum flow rate.
*Significance of differences in the same group before and after treatment is denoted as $P \leq .05$.

lack of clinical effect or worsening of health (aggravation of LUTS and/or suppression of sexual function). Division of these patients into groups was as follows: 13 (4.1%) patients in group A, 2 (0.6%) patients in group B, and 7 (2.2%) in group C. Another 10 (3.1%) patients dropped out because of side effects (4 persons each from groups B and C, 2 from group A), 6 (1.9%) patients because of recurrence of chronic diseases (1 from group A, 4 from group B, 1 from group C), 2 (0.6%) patients died because of cardiovascular diseases (both of them from group A), and 1 man from group C discontinued his participation without giving any reason. All patients who were discharged were included in the statistical analysis of the results.

RESULTS

Table 2 provides values of variables characterizing the functional status of LUT and sexual function at the start of and after end of treatment (at control point). According to MSHQ-EjD, ejaculator function significantly decreased in all 3 groups ($P \leq .05$). Satisfaction of sexual function in group C at control point is higher than before the treatment ($P \leq .05$). However, total score in each group before and after the treatment did not statistically significantly differ ($P \geq .05$).

According to IIEF, erectile function in all men who participated in the research did not change during the treatment. At control point was decrease of prostate gland volume in groups

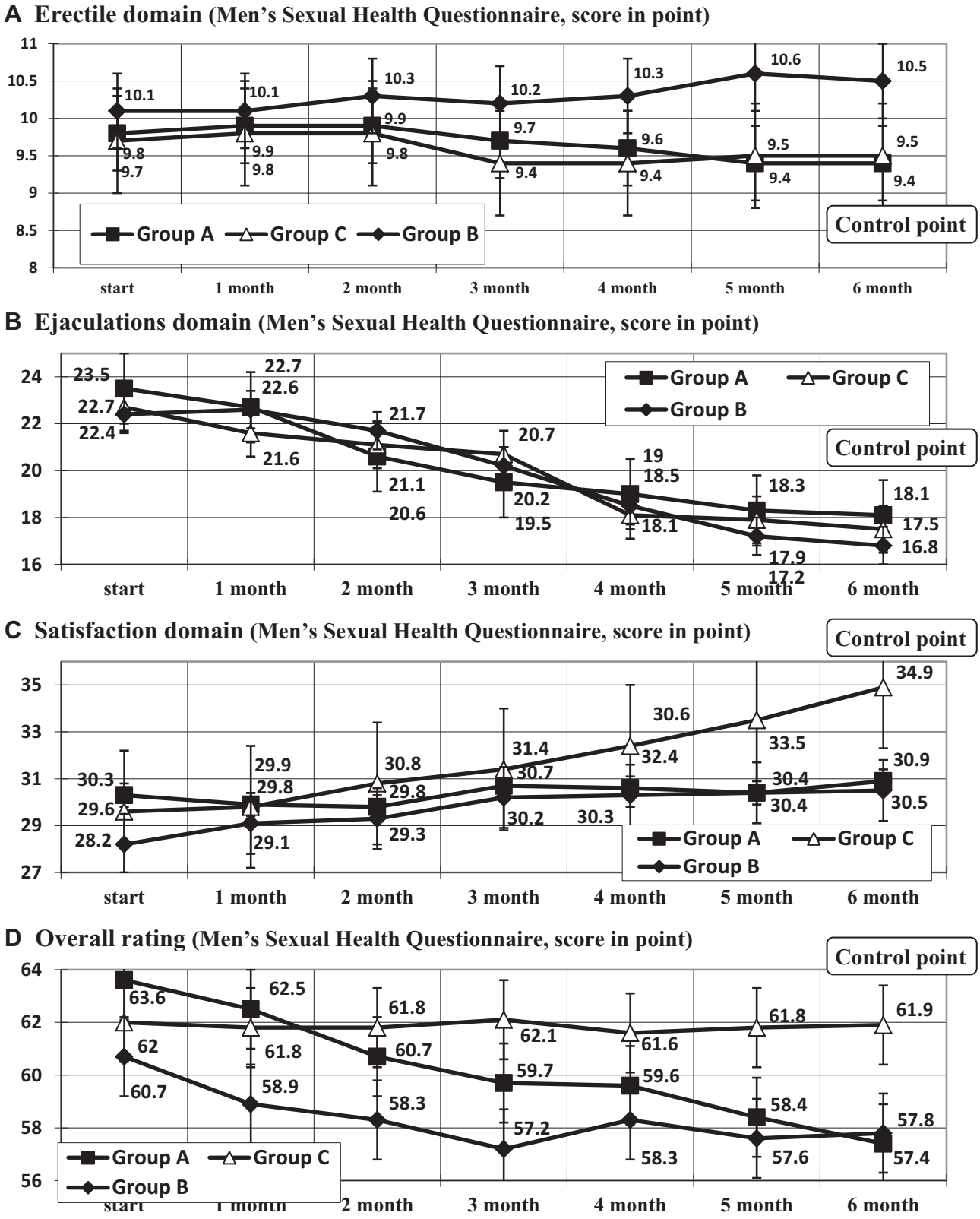

Figure 2. Changes in indicators of Men's Sexual Health Questionnaire in men with benign prostatic hyperplasia and lower urinary tract symptoms, who received combined treatment by dutasteride and solifenacin. Group A (N = 106) = acceptance of dutasteride 0.5 mg/d; group B (N = 99) = acceptance of dutasteride 0.5 mg/d and solifenacin 10 mg/d; group C (N = 112) = acceptance of dutasteride 0.5 mg/d and solifenacin 20 mg/d.

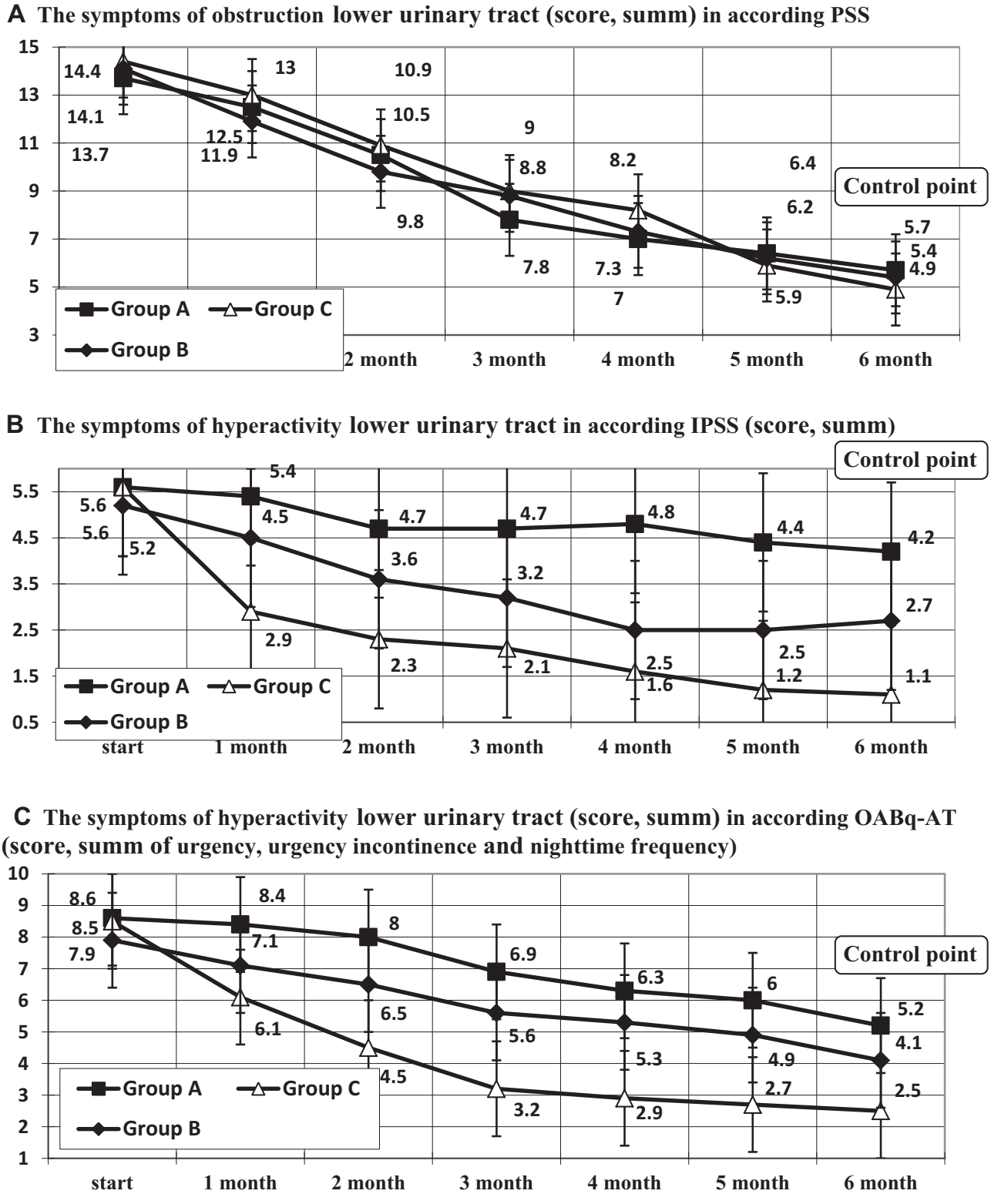

Figure 3. Changes in symptoms of obstruction and hyperactivity in lower urinary tract (International Prostate Symptom Score [I-PSS] and overactive bladder questionnaire—awareness tool [OABq-AT]) in men with benign prostatic hyperplasia and lower urinary tract symptoms, who received combined treatment by dutasteride and solifenacin. Group A (N = 106) = acceptance of dutasteride 0.5 mg/d; group B (N = 99) = acceptance of dutasteride 0.5 mg/d and solifenacin 10 mg/d; group C (N = 112) = acceptance of dutasteride 0.5 mg/d and solifenacin 20 mg/d.

A and B; the same tendency was registered for group C ($P \geq .05$).

Having rated the functions of LUT with the questionnaire I-PSS at control point, the following changes were detected (in comparison with the initial data). Significant decrease of intermittence was registered in all groups; incomplete emptying and weak stream were registered in groups B and C; and straining was registered in groups A and C (in all cases $P \leq .05$). However, the decrease of the level of specific symptoms of hyperactivity (urgency, nocturia) was detected only in men from group C. Urgency, nocturia, and incontinence significantly decreased in patients from group C according to the data of the OABq-AT as well ($P \leq .05$). Yet, the urgency significantly decreased in group B as well. According to diaries of urination, daytime and nighttime frequency of urination after the treatment was significantly less in men from group C; urgency was less in patients from groups B and C. Average flow rate after the treatment increased in patients of all 3 groups to normal values [A, 19.7 (3.4); B, 18.4 (2.6); C, 17.1 (3.1)]. Average value of post-void residual urine volume, on the contrary, decreased in patients of all groups (significantly only in groups B and C).

Figure 2 shows the data of changes of erectile and ejaculator functions at the control point of patients who took dutasteride and solifenacin for 6 months. Ejaculator function in all patients was decreasing simultaneously (groups A/B, r = 0.91, $P \leq .01$; groups A/C, r = 0.88, $P \leq .001$; groups B/C, r = 0.93, $P \leq .05$). Having assessed the ejaculator function, average score in all groups on the third month of observation (up to the end of the research) was less than initial one ($P \leq .05$). The rate of satisfaction of sexual function in men from group C at the end of the observation was significantly higher than initial one ($P \leq .05$), and significantly higher than the level in groups A and B at the end of the research ($P \leq .05$). General assessment of sexual function did not almost change at the end of the research ($P \geq .05$).

Figure 3 provides information on the monthly evaluation of the symptoms of urinary tract obstruction and urinary bladder hyperactivity in patients according to the I-PSS questionnaire and OABq-AT. According to the data obtained, symptoms of obstruction gradually and uniformly decreased in all 3 groups and reached a minimum at the reference point. Total number of points in evaluating the symptoms of obstruction at the reference point was significantly lower than at the beginning of the study (A, B, C: $P \leq .05$, $P \leq .05$, $P \leq .05$).

Symptoms of hyperactivity in group A at the reference point did not change significantly ($P \geq .05$). In groups B and C, these symptoms decreased and at the reference point were significantly less than at the beginning (B, C: $P \leq .05$, $P \leq .05$), but the rate and severity of changes were different. In group B, the level of symptoms of hyperactivity significantly decreased after 2 (I-PSS) and 3 (OABq-AT) months of observation. In group A, a significant decrease in the level of symptoms was noted already after the first month of observation (I-PSS: 5.6/2.9, $P \leq .05$; OABq-AT: 8.5/6.1, $P \leq .05$).

Figure 4 shows the results of rating of obstruction and hyperactivity symptoms in LUT the control point. The percentage of patients without pathological symptoms in group C was significantly higher (33.9%), than in 2 other groups (11.3%, 15.1%; $P \leq .01$, $P \leq .05$). On the contrary, in the group of men taking only dutasteride, the percentage of patients with moderate and several symptoms (25.5%) was significantly higher than in groups B and C (10.1%, 7.1%; $P \leq .05$, $P \leq .05$).

As already indicated, 2 people (1.9%) from group A discontinued treatment due to intolerable side effects (skin allergic reaction). Another 13 people (12.2%) from this group noted side effects: rash on head and neck, and itching on the feet and palms that disappeared themselves within 2–5 days. In group B, 4 people (4.0%) stopped treatment because they had intolerable dry mouth and persistent accommodation disturbance. Another 11 people (11.1%) from this group noted side effects: dry mouth, constipation, and allergic rash on the collar area and palms. In most patients, side effects disappeared within 2–7 days; in 2 cases, the treatment was interrupted for 5 days, and then resumed. 4 Patients (3.6%) in group C refused treatment because of side effects (dry mouth, diarrhea; in 1 case, oliguria). Another 21 people (18.7%) had side effects: dry mouth, dry sclera, constipation, and allergic reactions on the skin of extremities and head. In 15 patients (13.4%) side effects disappeared themselves within 2–5 days; in 6 cases the patients interrupted the treatment for 2–7 days. No additional treatment was required in any case. When comparing the percentage of patients with side effects between groups, no significant differences were found.

DISCUSSION

Despite intensive research having been done recently, the question of appropriate therapy adjustment for men with BPH and LUTS is still open. Though there are several classes of drugs decreasing the activity of growth factor of the prostate gland, we still have to resort to surgery in the treatment of BPH. It may be related with insufficient and/or irrational usage of the drugs.[9,31] Therefore, nowadays the active search of appropriate dosages and combinations of α1-adrenergic blockers, 5α-reductase inhibitors, phosphodiesterase type-5 inhibitors, and anti-muscarinic drugs is done to correct the volume of the prostate gland and to control the obstruction and hyperactivity symptoms of BPH.[16]

The study performed by us should have replied to a question: how effective the combination of dutasteride and solifenacin may be in the treatment of BPH with severe LUTS, and how the sexual function changes under the influence of these drugs. We found out that under the influence of the treatment the ejaculator function significantly decreases (regardless of whether men took solifenacin or not). By the way, a decrease of ejaculator function while taking 5α-reductase inhibitors is not surprising as

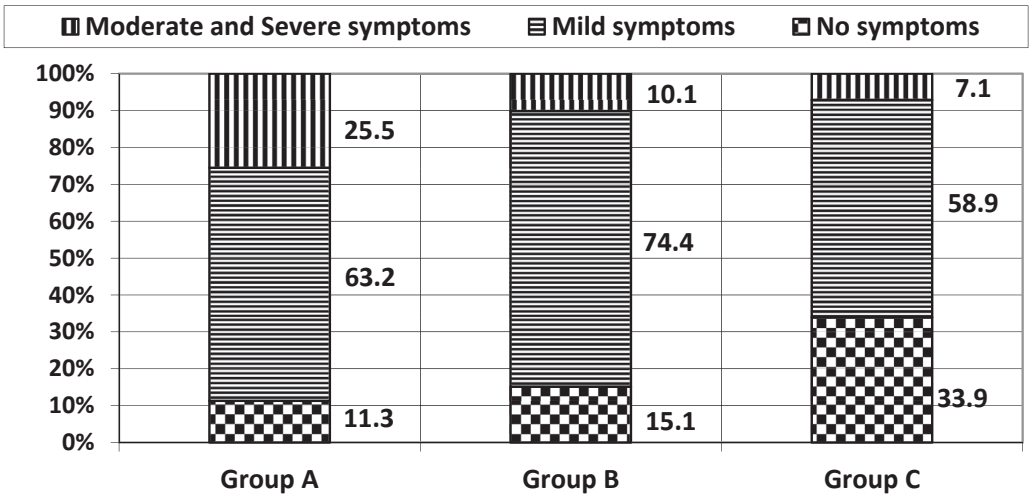

Figure 4. Percentage of patients with symptoms of obstruction and hyperactivity of the lower urinary tract after a 6-month course of treatment of combinations of dutasteride and solifenacin. Group A (N = 106) = acceptance of dutasteride 0.5 mg/d; group B (N = 99) = acceptance of dutasteride 0.5 mg/d and solifenacin 10 mg/d; group C (N = 112) = acceptance of dutasteride 0.5 mg/d and solifenacin 20 mg/d

it is directly related to mechanism of action of the drugs of this class. This effect is described by many authors, and some researchers suggest that reduction of the amount and changes in the quality of sperm does not have an influence on sexual function and sexual satisfaction.[19] We also found out that average score of the erectile function domain in each of 3 groups at the end of the research did not significantly differ from the initial one, which contradicts some reports in the literature.[16–18]

Interesting data were obtained in rating the domains of satisfaction and general sexual function. On the fifth and sixth months of observation the average score in these domains in men, having taken dutasteride and elevated dosage of solifenacin, was significantly higher than in patients from other groups ($P \leq .05$; $P \leq .05$). And if the average score in overall rating of sexual function in this group did not significantly differ from the initial one, then the score in the domain describing the sexual satisfaction was significantly higher than the initial one ($P \leq .05$).

Previously, some authors reported about the improvement in sexual function and quality of life associated with health in women with overactive urinary bladder after administration of anti-muscarinic medicines as a monotherapy (orgasm, 3.5 ± 0.3/4.5 ± 0.3; satisfaction, 2.6 ± 0.2/4.2 ± 0.3; desire, 2.5 ± 0.2/4.5 ± 0.2).[32,33] In other cases, it has been reported that combination of dutasteride and/or tamsulosin with anti-muscarinic drugs results in stabilization of sexual function (patients do not notice changes in erectile function)[34] and improves quality of life associated with health.[11,23,25,35] At the same time, new data on pathogenesis of LUTS and mutual influence of pathogenesis of LUTS and BPH have recently been obtained. Studies on experimental models in animals have shown that artificial disturbance of macro- and micro-circulation in pelvic organs can lead to ischemia of the urinary bladder and adjacent organs. As a consequence, oxygen tension decreases, oxidative stress develops, activity of the cholinergic receptors increases, and ultra-structure of the neurons of pelvic organs is damaged.[36] Several other studies indicate that disturbance of normal blood supply can contribute to formation of LUTS in both men and women through ischemia, hypoxia, and oxidative stress.[8,25,37] Currently, there are also suggestions that disturbance of oxygen tension in tissues due to changes in micro-circulation and subsequent hypoxia may be associated with development of metabolic syndrome in pelvic organs. Meanwhile, metabolic syndrome, including disturbance of lipid metabolism, hyperlipidemia, and, in particular, increased cholesterol levels, is an important link in the formation of BPH.[8] Thus, both atherosclerotic processes in the vessels of small pelvis and spasm of smooth muscles contribute to decrease in normal blood supply to pelvic organs.

However, inhibition of activity of muscarinic receptors by solifenacin reduces the tone of smooth muscle in detrusor and adjacent pelvic organs.[38] Effect of this medicine depends, in part, on the dose taken. Thus, in our opinion, it is appropriate to assume that high doses of solifenacin ultimately provide a sufficient level of oxygenation for appearance of a clinical effect. It was in group C, in patients receiving increased dose of solifenacin, where a significant increase in satisfaction with sexual intercourse, including due to the strength and "brightness" of orgasm, was observed. Perhaps a significant increase in oxygenation and trophism in general of those nerve structures that provide a discharge of sexual arousal and increased level of afferent signals have a similar result. Preservation of erectile function is of great importance; according to our data, its decrease against the background of combined therapy was unreliable.

Another possible variant of explanation of the obtained results, in our opinion, is in the field of psychology of assessing health condition and the perception of the quality of life associated with

health. As previously shown, increased doses of solifenacin while rapidly reducing symptoms such as nocturia, urgency, and increased daytime and nighttime frequency of urination significantly improves the quality of life associated with health and observance of the treatment.[39,40] According to the data of Medical Outcomes Study-Short Form (MOS SF-36) questionnaire, administration of anti-muscarinic medicines leads to significant increase in both average score in domains of vitality, physical functioning, general health perceptions, emotional role functioning, mental health, and self-assessment of mental and physical health in general. Perhaps reconverting from obsessive and irritating symptoms of urgency, sometimes leading to reactive depression, patients partially extrapolate increased assessment of urinary tract function on quality and satisfaction with sexual function.

Perhaps both variants of the explanation to some extent complement each other. However, of course, exhaustive understanding of the mechanism of influence of dutasteride and increased doses of solifenacin on the function of sexual satisfaction requires increase in the volume of data and further research.

As already mentioned, the proposed treatment option did not affect the decrease of ejaculatory function typical for 5α-reductase inhibitors, which is quite natural: with direct inhibition of the 5α-deoxyhydrotestosterone synthesis function. At the same time, erectile function decreased unreliably. Perhaps this happened against the background of compensation of hormonal deficiency with the same anti-spasmodic effect of solifenacin, increased blood flow, and increased oxygenation of intramural vegetative neurons of pelvic organs. At the same time, there was a rapid reverse development of symptoms of hyperactivity in the group of men administering increased doses of solifenacin, which could positively affect perception of the treatment in general, and the function of sexual satisfaction in particular, as well as increase observance of the treatment, which is a serious problem with long-term courses of therapy.

Recent studies have confirmed the almost identical effectiveness of solifenacin and mirabegron in the restoration of LUT function, which worsened after long intake of dutasteride.[35] In this study, we showed that simultaneous intake of dutasteride and elevated dosages of solifenacin can not only improve the function of LUT, but also lead to the reduction of sexual dysfunction, and increase sexual satisfaction in men with BPH and severe LUTS. However, our data suggest that at least in some cases the combination of 5α-reductase inhibitors and solifenacin in elevated dosage is enough to correct BPH with severe LUTS effectively. Such a combination can allow avoiding excessive side effects and polypharmacy.

Obtained data on reversibility of obstruction and hyperactivity symptoms correspond to the literature data for each of these drugs.[15,16] Manifestations of such symptoms as intermittence straining were decreased in patients of all groups, the volume of prostate gland was reduced, and the average and maximal urine flow rate increased. However, along with these changes, the manifestations of weak stream, urgency, urgency incontinence, and nighttime frequency decreased in group C. Generally, according to uroflowmetry, diaries of urination, and OABq-AT and I-PSS questionnaire, intake of double dosage of solifenacin combined with dutasteride in patients with BPH and severe LUTS is considered to be proven and rational. The safety of elevated dosage of solifenacin was also shown earlier.[12–14]

Summarizing the data obtained, we would like to note the following points. It is known that dutasteride is effective for the treatment of BPH, with its long-term use, the volume of the prostate gland decreases, and symptoms of obstruction decrease or disappear. Simultaneously, action of this medicine suppresses the synthesis of deoxyhydrotestosterone, which results in deterioration of ejaculatory, erectile functions; reduced satisfaction from sexual intercourse; and reduced libido. Effect of solifenacin on LUTS is also considered to be well studied, and its effectiveness and safety are proven. However, the combined effects of these medicines for BPH and severe LUTS have not been studied previously. As a result of the study, we found out that when patients administer dutasteride and increased dose of solifenacin at a reference point ejaculatory function worsens in accordance with expectations, but erectile function does not differ significantly from baseline, and sexual satisfaction of patients significantly increases. In addition, manifestations of symptoms of hyperactivity significantly decrease after the first month of treatment, and remain at low level at the reference point. Based on the analysis, we hypothesized that elevated doses of solifenacin relieve spasm of smooth muscles of the detrusor and adjacent pelvic organs. This leads to improvement of microcirculation and increased oxygenation of tissues, which may partially compensate for the effect of reduction of the synthesis of dihydrotestosterone and decrease of erectile function, and also stimulates afferent nerve structures, enhancing orgasm. We also suggested that rapid reverse development of severe symptoms of hyperactivity (usually obsessive and irritating) can return the patient to a zone of psychological comfort. However, it is possible that he can extrapolate the quality of life associated with health on the function of sexual satisfaction.

This research is limited. We did not study late results of the combined therapy. Nevertheless, it is known that long intake of anti-muscarinic drugs and 5α-reductase inhibitors is associated with the problems of adherence and can be accompanied by refusal of treatment in some patients.[40] A reason to refuse the therapy can be a lack of effectiveness, and on the contrary relief of obstruction and hyperactivity symptoms, and the whole range of social and psychological factors. Thus, to assess accurately the survival (persistence, safety) of the effects it is necessary to run further long-term studies. The study of the effect of the combination of dutasteride and solifenacin on human beings older than 65 years also can be an objective of further research as

elderly men are quite specific cohort of patients; they are more amenable to side effects while taking 5α-reductase inhibitors and have age-related changes of cognitive functions. Studying variability of cognitive function with long-term intake of the combination of 5α-reductase inhibitors also can be continued in further research.

Nevertheless, to our mind obtained data can contribute in effectiveness assessment and safety of combined therapy of BPH and LUT, and can be used in the practice of urologists, neurourologists, and allied physicians to adjust appropriate therapy in patients with BPH and severe LUTS. For example, in the event of intolerance to phosphodiesterase type-5 inhibitors, polypharmacy, and absence of symptoms on decrease in sexual function to practitioner, information that a high dose of solifenacin administered concomitantly with dutasteride may contribute to increase in sexual satisfaction and preservation of erectile function at the baseline level can be useful.

CONCLUSION

Overall sexual function in men with BPH and severe LUTS is not impaired by prolonged intake of double dosage of solifenacin combined with dutasteride. Sexual satisfaction of men at the end of the sixth month of combined therapy course becomes higher than the initial one. This combination does not impact on erectile function but fractionally decreases ejaculation function. However, the overall assessment of sexual function by patients is quite high. The combination of dutasteride and doubled dosage of solifenacin causes a rapid reversibility of obstruction and hyperactivity symptoms typical for BPH with severe LUTS and is not accompanied with the increase of side effects.

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