

Adverse Effects of Pharmacological Therapy of Benign Prostatic Hyperplasia on Sexual Function in Men

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SUMMARY

Introduction The development of effective medications makes pharmacological therapy of BPH the dominant mode of treatment today. It improves urinary symptoms and prevents disease progression while producing side effects on male sexual function.

Objective The aim of the study is to present the effects of BPH pharmacological treatment on the occurrence of sexually adverse effects in men: changes in sexual desire, erectile, ejaculatory and the orgasmic function.

Methods A prospective study involving 156 BPH patients. The average age was 61.16±2.97. Four groups of 39 patients each were formed. The 4 groups were administered tamsulosin (alpha-blocker), finasteride (5-alpha reductase inhibitor), combination therapy (tamsulosin and finasteride) respectively, while the control group received no treatment. IPSS-QoL, IIEF and MSHQ-EjD questionnaires were used to evaluate the symptoms of voiding and sexual function. Follow-up examinations were performed 3 and 6 months into treatment.

Results Voiding symptoms improved in all groups receiving therapy. The side effects on the sexual function in all these groups include significant disorders of ejaculation and the orgasmic function. Ejaculation disorders: tamsulosin (-4.38±2.55; p<0.001), combined therapy (-3.89±2.84) and finasteride (-1.49±2.52). Orgasmic function disorders: tamsulosin (-1.03±1.94), combined therapy (-0.76±2.07) and finasteride (-0.54±1.68). Complete absence of ejaculation was experienced by 23% of patients on combined therapy, 15% on tamsulosin and 5% on finasteride.

Conclusion Pharmacological therapy of BPH improved voiding symptoms producing different effects on male sexual function. The main adverse effect on sexual function in men is the deterioration in ejaculation or the absence thereof. Clinical consideration of BPH should include the elements of male sexual function, patients' age, the characteristics and effects of each group of drugs.

Keywords: prostate; ejaculation; erection; orgasm; sexual desire

INTRODUCTION

Benign prostatic hyperplasia (BPH) implies prostate enlargement accompanied by lower urinary tract symptoms (LUTS). The aim of BPH treatment is alleviating urination problems, preventing disease progression and improving the quality of life [1]. The main principle of treatment has significantly changed in recent years from the earlier approach that relied solely on surgery rather than on drug therapy [2]. The reason for this is the development of effective drugs for solving the dynamic and static components of the obstruction in the prostate and the urinary bladder neck, as well as the knowledge of bladder physiology [3].

However, a series of studies conducted in the 1990s showed that despite the improvement of urinary symptoms there were also adverse effects of drug therapy of BPH [4]. It was the occurrence of the elements of sexual dysfunction (SD), or the inability to achieve satisfactory sexual relationship in any of its phases. Clinical forms of SD are: erectile dysfunction

(ED), ejaculatory and orgasmic disorders and sexual desire disorders [5].

The applicable protocols for pharmacological therapy of BPH recommend the use of alpha-blockers (AB) and 5-alpha reductase inhibitors (5ARI), individually or in combination. This therapy may be associated with sexually adverse effects, with different effects being produced by different groups of drugs or drugs within the same group [6]. In patients without clinical symptoms of obstruction, experiencing mild symptoms, the active monitoring approach is applied (Watchful Waiting – WW) [1, 7].

AB bind to alpha-1 receptors, relax the smooth muscles of the prostate and bladder neck, enhance the urine flow and facilitate urination. They do not lead to a reduction in prostate size nor do they prevent disease progression. They differ in uroselectivity and the production of adverse effects [8]. They frequently contribute to the decline of libido and ED similar to that of a placebo, while having different effects on ejaculation. They can be non-selective (Doxazosin, Terazosin, Alfu-

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zosin) and selective (Tamsulosin, Silodosin). Tamsulosin is a third generation AB with a higher affinity for prostatic receptors (alpha-1A) than for the receptors in smooth muscles of blood vessels (alpha-1B) that rarely causes hypotension [9].

5ARI cause the inhibition of 5-alpha reductase enzymes and block the conversion of non-active forms of testosterone into dihydrotestosterone (DHT), which is responsible for prostate enlargement [10]. It is available in two forms – finasteride and dutasteride – with similar clinical effects. They produce sexual side effects and increased risk for ED, ejaculatory dysfunction (EjD) and decreased libido compared to a placebo [11].

The third mode of treatment, the combination of AB and 5ARI incorporates the combined effect of both components. They produce sexual side effects, which combine the side effects of these individual drugs [12].

OBJECTIVE

The aim of this study is to present the results concerning the effects of drug therapy on the occurrence of BPH sexual side effects in men: changes in sexual desire, erectile and ejaculatory function and the orgasmic function.

METHODS

A prospective clinical study was conducted at the Urology Department of the Military Hospital in Nis during 2011 and 2012. A total of 156 BPH patients of average age of 61.16 ± 2.97 took part. The patients had not been previously treated for BPH, were sexually active and had no significant comorbidities. They were informed about the research goals and all signed the consent note to participate in the research. The Ethics Committee of the Military Hospital in Niš approved the implementation of research.

All the patients underwent a clinical examination conducted per diagnostic protocol for BPH. Following anamnesis and digito-rectal examination, biochemical analyses were performed for PSA and fPSA blood markers. A urine culture test with an antibiogram, urinary tract ultrasonography and uroflowmetry were performed. The patients were then asked to fill out standardized questionnaires measuring urinary symptoms and sexual function.

The intensity of urination symptoms was measured using the International Prostate Symptom Score (IPSS-QoL) containing seven questions (scoring 0–5). It is included in all treatment protocols and examines urinary symptoms in the past month [1, 7]. Four questions examine obstructive symptoms (emptying, intermittency, straining, weakness), while the remaining three refer to irritative symptoms (frequency, urgency, nocturia). The score is evaluated as: (0–7) mild symptoms, (8–19) moderate symptoms, (20–35) severe symptoms. The additional question is about the quality of life (QoL) (grades 0–6).

Sexual function was measured by the International Index of Erectile Function (IIEF) questionnaire with 15

questions (scored 0–5). It assesses the elements of sexual function in the past month. It has been recommended since 1999 by the World Health Organization (WHO) as an efficient way to measure the results of the SD treatment [13]. It assesses five elements: 1) Erectile function – 6 questions (ratings ranging from ‘very difficult’ to ‘normal erections’); 2) Orgasmic function – 2 questions (ratings ranging from ‘very difficult’ to ‘normal orgasm’); 3) Sexual desire – 2 questions (ratings ranging from ‘complete absence of sexual desire’ to ‘constant desire’); 4) Intercourse satisfaction – 3 questions (ratings ranging from ‘never satisfied’ to ‘completely satisfied’); 5) Overall satisfaction with sex life – 2 questions (ratings ranging from ‘never satisfied’ to ‘completely satisfied’).

For a more complete assessment of the ejaculatory function Male Sexual Health Questionnaire-Ejaculatory Dysfunction (MSHQ-EjD) was used. (User Agreement-MSHQ #1886, Mapi Research Trust, Lyon, France). It includes four questions (scores 0–5) as suggested by Rosen et al. [14], and is widely used to evaluate the EjD in clinical trials. Characteristics of ejaculation were evaluated through 3 questions: frequency (from ‘total absence’ to ‘constant presence’), the strength of ejaculation (from ‘total absence’ to ‘normal strength’) and the volume of ejaculation (from ‘total absence’ to ‘normal amount’). The fourth question evaluates the concern about the ejaculation condition (from ‘no problem’ to ‘extremely bothered’).

The criterion for taking part in the study was the presence of mild to moderate urinary symptoms (IPSS < 20), prostate tissue weighing > 30 g, PSA < 4 ng/mL. Patients with BPH complications – potential malignancy, residual urine > 200 ml, infections, bladder calculus and obstructive changes in kidneys – were excluded.

Four groups of 39 patients were formed. The first group of patients received tamsulosin 0.4 mg/day (AB), the second received finasteride 5 mg/day (5ARI), the third group used combination therapy (tamsulosin and finasteride) while the control group received no treatment. After 3 and 6 months of therapy, follow-up examinations were performed and the questionnaires completed the same way it was done prior to the study. All the results were compared within each group and also between the groups.

Tamsulosin was administered to patients with prostate weights < 40 g, and finasteride to patients with prostate weights of 40–50 grams. Patients with prostate weight > 50 g, and the greatest risk of disease progression used combination therapy. Treatment groups had more severe urination difficulties ($7 < \text{IPSS} < 20$) than patients in the control group ($\text{IPSS} < 8$).

The values of all scores are shown as a mean value \pm standard deviation. The degree of statistical significance was $p < 0.05$. The differences between the scores were tested through the analysis of variance for repeated measuring (RM ANOVA). The comparison of changes in score values for three treatment groups and the age of patients in all four groups was made using a one-way ANOVA variance analysis and the post-hoc Tukey test.

RESULTS

The average patient age in each group was as follows: tamsulosin group 60.69 ± 3.22 , finasteride group 61.56 ± 3.30 , combined therapy group 61.76 ± 2.51 , and 60.64 ± 2.70 in the control group. There were no statistically significant differences pertaining to age structure between compared groups.

All treatment groups experienced a significant improvement in urinary symptoms (IPSS), with the most significant progress experienced by the group on combined therapy (-10.95 ± 3.19 ; $p < 0.001$) with a significantly greater change compared to patients who only used finasteride (-9.00 ± 2.84 ; $p < 0.001$) or tamsulosin (-5.84 ± 3.08 ; $p < 0.001$). The control group experienced no significant changes.

Assessing the elements of sexual function (IIEF questionnaire) showed that libido or sexual desire as a biological need for sexual activity had not significantly changed after 6 months of treatment. In patients on finasteride there was slight deterioration (-0.54 ± 1.68), while the combined therapy group experienced slight improvement (0.27 ± 1.81). In the tamsulosin group there was a significant improvement in sexual desire (0.78 ± 1.00 ; $p < 0.001$). This is a significant change compared to the group on finasteride but not compared to the group on combined therapy (Graph 1).

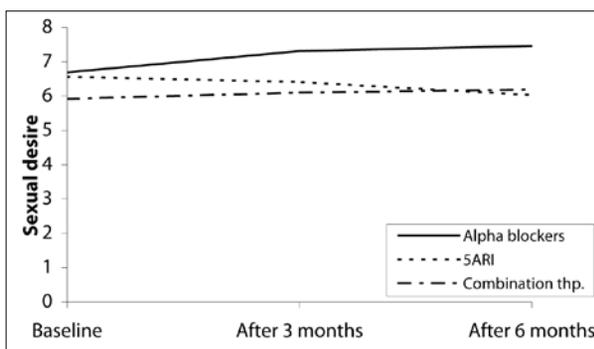
The erectile function did not decline; just the opposite, it significantly improved in treatment groups (Graph 2). The greatest improvement occurred in patients on tamsulosin (2.46 ± 3.73 ; $p < 0.001$), followed by the group on combined therapy (2.19 ± 5.14 ; $p = 0.014$), and the group on finasteride (1.64 ± 4.96 ; $p = 0.046$).

The orgasmic function deteriorated in all groups (Graph 3). The greatest deterioration occurred in the tamsulosin group (-1.03 ± 1.94 ; $p = 0.003$), followed by the combined therapy group (-0.76 ± 2.07 ; $p = 0.033$), statistically significant for both groups. Significant deterioration occurred after 3 months of treatment. The least deterioration with no significance was experienced by patients who only received finasteride (-0.54 ± 1.68).

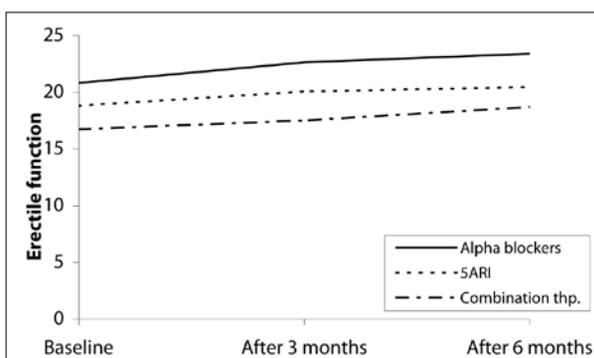
Answers to the MSHQ-EjD questionnaire showed ejaculatory function significantly deteriorated in all treatment groups after 6 months of therapy (Table 1). The greatest deterioration was for patients on tamsulosin (-4.38 ± 2.55 ; $p < 0.001$), followed by the combined therapy group (-3.89 ± 2.84 ; $p < 0.001$). No significant differences were found between these changes, although they were significantly higher ($p < 0.001$) than in patients using finasteride (-1.49 ± 2.52). Significant changes in the deterioration occurred in both groups after 3 months of therapy (Graph 4).

One significant sexual side effect was the complete absence of ejaculation. This was most common in the combined therapy group – occurring in 23% (9 patients), in tamsulosin group in 15% (6 patients), and in the group on finasteride occurring in 5% (2 patients).

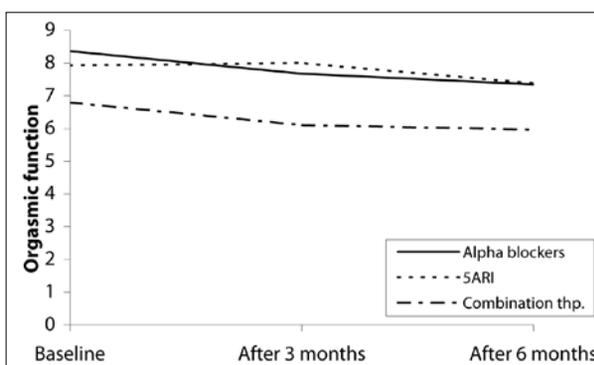
Bother score concerning the ejaculation condition significantly deteriorated in all treatment groups after 6 months (Table 2). The greatest deterioration was in the tamsulosin group (1.86 ± 1.62 ; $p < 0.001$), followed by the combined therapy group (1.41 ± 1.61 ; $p < 0.001$) and finasteride patients



Graph 1. Sexual desire



Graph 2. Erectile function



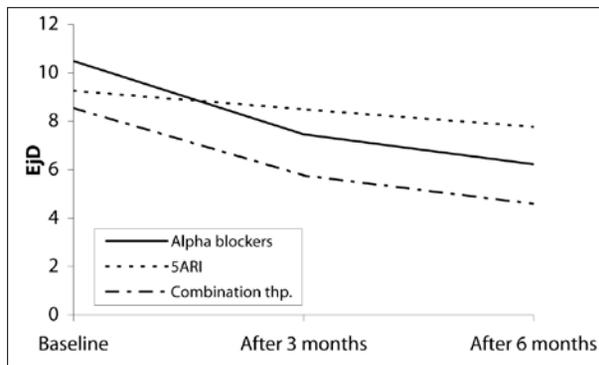
Graph 3. Orgasmic function

Table 1. Changes in ejaculatory function (number of patients)

Therapy group	Ejaculatory function			Total
	Improvement	Aggravation	No change	
Tamsulosin	-	25 (64%)	14 (36%)	39
Finasteride	5 (13%)	15 (38%)	19 (49%)	39
Combination therapy	3 (8%)	23 (59%)	13 (33%)	39
Control group	12 (31%)	2 (5%)	25 (64%)	39

Table 2. Changes in bother over ejaculatory dysfunction condition (number of patients)

Therapy group	Degree of bother			Total
	Increasing	Declining	No change	
Tamsulosin	13 (33%)	2 (5%)	24 (62%)	39
Finasteride	6 (15%)	12 (31%)	21 (54%)	39
Combination therapy	11 (28%)	5 (13%)	23 (59%)	39
Control group	-	3 (8%)	36 (92%)	39



Graph 4. Ejaculatory dysfunction

(0.56 ± 1.43 ; $p=0.001$). The deterioration in the tamsulosin group was significantly higher than the change in the finasteride group, but not compared with the combined therapy group. Significant deterioration of the bother score occurred in the tamsulosin group and the combined therapy group after 3 months of therapy (Graph 5).

No significant changes in all elements of sexual function were reported by the control group after 6 months.

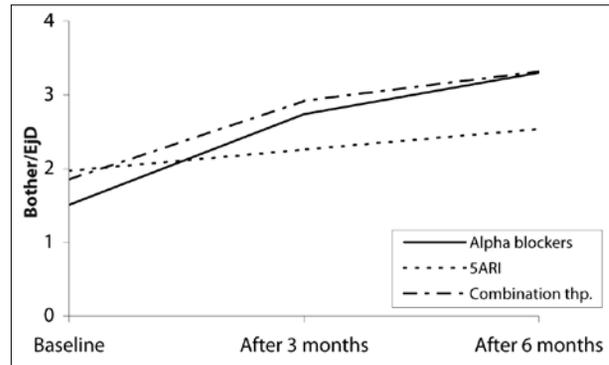
DISCUSSION

By the end of testing, urinary symptoms in treatment groups had showed significant improvement of IPSS-QoL scores. In addition to the desired therapeutic effect, the major sexual side effect of the observed drugs was significant deterioration in ejaculation, or the absence thereof, and deterioration in the orgasmic function. All of these could cause serious psychological and social problems in patients.

Erection is a vasocongestive response of erectile tissue to the variety of stimuli that produce penile rigidity sufficient for vaginal penetration [15]. It improved in all 3 treatment groups. Patients with severe urinary symptoms often identified relief in the act of urination with improved erectile function.

Ejaculation takes place in two phases. In the first, emission phase sympathetic spinal reflexes lead to contractions of the ductus deferens. By reflex, spermatic fluid is ejected in the posterior urethra. In the second, expulsion phase, volitional control is lost. Rhythmic contractions of the pelvic floor muscle and the relaxation of urethral sphincter take place. Spermatic fluid is evacuated outside from the urethra [16].

Ejaculation disorders were most frequent in the tamsulosin group – in 64% of patients. These disorders are manifested in the reduced number of ejaculations during sexual activity and the reduced amount of semen ranging to complete absence of ejaculate (in 15% of patients). Before orgasm, the pressure in the urethra proximally to the verumontanum culminates. Therefore, semen travels to a place of lower pressure toward the external urethral orifice [17]. However the effect of the uroselective tamsulosin relaxes the tone of smooth muscles of the bladder neck. Thus it reduces the pressure proximally to the verumontanum and retrograde ejaculation occurs [9].



Graph 5. Bother/ejaculatory dysfunction (EjD)

In this group, there was the greatest increase of the degree of bother about the ejaculation condition (33%) and the worst deterioration in the orgasmic function compared to other treatment groups. An orgasm is a feeling of intense pleasure which accompanies ejaculation. It is a consequence of the cerebral processing of sensory stimuli from the posterior urethral field and contractions of accessory sex organs [18]. Due to the reduced amount of the ejaculate, sometimes ranging to its complete absence from the emission phase, the extent of sensory stimuli coming from posterior urethra, which leads to the orgasmic feeling, is reduced.

In the group using finasteride ejaculation exacerbated in 38% of patients mainly due to the decreased ejaculation strength (assessment ranged from 'barely ejaculating' to 'considerably weaker ejaculation'). Complete absence of ejaculation occurred in 5% of patients. The bother condition exacerbated in 15% of patients but was significantly lower compared to the other 2 groups. In this group there was no significant decrease of sexual desire, which is usually listed as a characteristic of this group of medications, in much larger studies [19]. The orgasmic function in the finasteride group was significantly reduced, but this deterioration was less compared to the other 2 groups.

According to the American Urological Association (AUA) AB effect on EjD is as follows: selective up to 28%; nonselective <1.5%. Regarding finasteride – the incidence of ED was 8%, the decline of libido 5% and EjD 4% [7].

Gacci et al. [20] claim tamsulosin is associated with a higher incidence of EjD (10%) compared to other ABs (0–1%). Daily tamsulosin dose of 0.8 mg reduced the average ejaculate volume in almost 90% of respondents, while 35% had no ejaculation at all. As AB gets more effective over time, incidence of EjD increases. The combination of AB and 5ARI triples the risk for EjD incidence compared to that of AB or 5ARI used individually. Finasteride bears the same risk as dutasteride for causing EjD [20].

Kim et al. [21], in a study involving 138 men over 50, reported that 3 months of tamsulosin 0.2 mg use produced no significant effect on sexual function nor a negative impact on the ejaculation function. Our results indicate that the use of 0.4 mg of tamsulosin for a period of 3 months led to a significant deterioration in the ejaculatory function and the orgasmic function.

Clinical trials show that 5ARI lead to ED in 3–16% of patients, decline or loss of libido in 2–10%, EjD in 0–8%

[22]. EjD has not been sufficiently researched concerning the use of 5ARI. The reduction of DHT caused by 5ARI administration is associated with decreased sexual desire and orgasm [23].

In the view of Corona et al. [24], the impact of 5ARI is associated with an increased risk of reduced sexual desire, whereas no connection with ED and EjD was found. The use of 5ARI in men with a SD does not significantly worsen the already existing ED and EjD, although it can further aggravate their sex life by reducing sexual desire and spontaneous erections.

Trost et al. [25], in the analysis of randomized trials, concluded that compared to a placebo, 5ARI accounted for decreased libido (1.5%), ED (1.6%), EjD (3.4%) and gynecomastia (1.3%).

Kaplan et al. [26], in a 5-year evaluation study of the effect of finasteride and dutasteride, reported that the incidence of ED, EjD and the reduction in libido was higher with dutasteride (5.1%, 2.4%, 2.7%) compared to finasteride use (2.1%, 1.8%, 1.4%). Finasteride and dutasteride are equally effective in the treatment of LUTS.

In the group on combined therapy the orgasmic function declined significantly, although less than in the group on tamsulosin. Ejaculation function worsened in 59% of patients due to reduced incidence of ejaculation and ejaculation strength as well as the reduced amount of semen. Complete absence of ejaculation occurred in 23% of patients, which is higher than in the tamsulosin group. The degree of bother with the ejaculation condition significantly deteriorated although less than in the group on tamsulosin. Urination difficulties were more common in the group on combined therapy, which is probably why after 6 months of therapy this group experienced the greatest improvement in the IPSS score.

Sexual desire in the group on combined therapy was without any significant changes. Erectile function improved significantly despite significant deterioration of ejaculation. In this group the overall satisfaction with sex life improved according to IIEF questionnaire. This means that the problems with ejaculation were not perceived as negative as the problems with erectile dysfunction [27].

Combat study on tamsulosin and dutasteride involving 4,844 men showed that the degree of ED after 24 months was 3.8% on tamsulosin, 6.0% on dutasteride and 7.4% on combined therapy. Retrograde ejaculation, the absence of

ejaculation and weakening of sexual desire occurred in 1.1%, 0.8% and 1.7% of patients on tamsulosin; in 0.6%, 0.5% and 2.8% on dutasteride; and in 4.2%, 2.4% and 3.4% on combined therapy. This means that the overall side effects are significantly more common during combination therapy than during monotherapy administration. Similarly, compared to monotherapy involving AB and 5ARI, combination therapy led to greater improvement in urinary symptoms and better prevention of diseases progression [28].

The results of this study are consistent with most results obtained by other authors. They show that the deterioration in ejaculation or the absence thereof is the main sexual side effect of drugs used for the treatment of BPH.

In dealing with the patients, it is important to explain in advance the possible side effects of medications on the sexual function. Patients are then more willing to accept these effects. In 2011 Mirone et al. [29] proposed an appropriate algorithm for the treatment and follow-up of such patients with the purpose of comprehensive and accurate perception of SD caused by BPH. Patients should be involved in making decisions about the treatment, bearing in mind that the risk is more significant in younger men [30].

CONCLUSION

Available options for pharmacological treatment of BPH improve urinary symptoms but do not have the same effect on the elements of sexual functions in men. The main adverse effect on sexual function in men is the deterioration in ejaculation or the absence thereof. Clinical consideration of men with urinary symptoms caused by BPH should initially include the assessment of sexual desire, erectile and ejaculatory function. Patients' age and the characteristics of each group of drugs and their effect should particularly be taken into consideration.

NOTE

This paper is a part of a research activity within the primary author's PhD thesis titled "The impact of medical treatment of benign prostatic hyperplasia on sexual life, function and lower urinary tract symptoms", which was defended at the University of Niš Faculty of Medicine in 2014.

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Нежељени ефекти фармаколошке терапије бенигне хиперплазије простате на сексуалну функцију мушкараца

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КРАТАК САДРЖАЈ

Увод Фармаколошка терапија бенигне хиперплазије простате (БХП) постаје доминантан начин лечења захваљујући развоју ефикасних лекова. Упркос побољшању уринарних симптома и спречавању напредовања болести, проузрокује нежељене ефекте на сексуалну функцију мушкараца.

Циљ рада Циљ рада је био да се прикажу резултати фармаколошког лечења БХП на појаву сексуалних нежељених ефеката код мушкараца: промене сексуалне жеље, ерекtilне и ејакулаторне функције, као и функције оргазма.

Методе рада Урађена је проспективна студија са 156 болесника са БХП, просечне старости 61,16±2,97 година. Образоване су четири групе од по 39 испитаника. Једна група је примењивала тамсулосин (алфа-блокатор), друга финастерид (инхибитор 5-алфа редуктазе), трећа комбиновану терапију (тамсулосин и финастерид), док је контролна група испитаника била без терапије. Симптоми мокрења и сексуалне функције су оцењивани упитницима *IPSS-QoL*, *IIEF* и *MSHQ-EJD*. Контроле су рађене након три месеца и шест месеци лечења.

Резултати Симптоми мокрења су побољшани у свим терапијским групама. Од нежељених ефеката на сексуалну функцију, у свим терапијским групама забележени су значајни поремећаји ејакулације и функције оргазма. Поремећаји ејакулације били су следећи: са тамсулосином -4,38±2,55 ($p<0,001$), комбинованом терапијом -3,89±2,84 и финастеридом -1,49±2,52. Поремећаји функције оргазма били су: са тамсулосином -1,03±1,94, комбинованом терапијом -0,76±2,07 и финастеридом -0,54±1,68. Потпуни изостанак ејакулације након примене комбиноване терапије забележен је код 23% болесника, након примене тамсулосина код 15%, а финастеридом код 5%.

Закључак Фармаколошко лечење БХП побољшава симптоме мокрења с различитим ефектом на сексуалну функцију мушкараца. Главни нежељени ефекат на њихову сексуалну функцију је погоршање ејакулације или њен изостанак. При клиничком разматрању БХП треба узети у обзир елементе сексуалне функционалности код мушкараца, животну доб и особине дејства сваке групе лекова.

Кључне речи: простата; ејакулација; ерекција; оргазам; сексуална жеља