https://doi.org/10.17816/uroved10167-74

PHOSPHODIESTERASE TYPE 5 INHIBITORS IN TREATMENT OF LOWER URINARY TRACT DYSFUNCTIONS

© *I.V. Kuzmin, A.Kh. Ajub, M.N. Slesarevskaya*

Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia

For citation: Kuzmin IV, Ajub AKh, Slesarevskaya MN. Phosphodiesterase type 5 inhibitors in treatment of lower urinary tract dysfunctions. *Urology reports (St. Petersburg)*. 2020;10(1):67-74. https://doi.org/10.17816/uroved10167-74

Received: 14.01.2020 Revised: 20.02.2020 Accepted: 19.03.2020

The article provides a review of current data on the pharmacological and pathogenetic principles of the use of selective type 5 PDE inhibitors in patients with lower urinary tract dysfunctions. The mechanisms of the therapeutic action of these drugs for various urinary tract dysfunctions are examined in detail, the leading of which is the improvement of blood circulation and the reduction of ischemia of the pelvic organs.

Keywords: phosphodiesterase type 5 inhibitors; lower urinary tract dysfunctions; ischemia of the pelvic organs; tadalafil.

ИНГИБИТОРЫ ФОСФОДИЭСТЕРАЗЫ 5-го ТИПА В ЛЕЧЕНИИ ДИСФУНКЦИЙ НИЖНИХ МОЧЕВЫХ ПУТЕЙ

© *И.В. Кузьмин, А.Х. Аюб, М.Н. Слесаревская*

Федеральное государственное бюджетное образовательное учреждение высшего образования «Первый Санкт-Петербургский государственный медицинский университет им. академика И.П. Павлова» Министерства здравоохранения Российской Федерации, Санкт-Петербург

Для цитирования: Кузьмин И.В., Аюб А.Х., Слесаревская М.Н. Ингибиторы фосфодиэстеразы 5-го типа в лечении дисфункций нижних мочевых путей // Урологические ведомости. – 2020. – Т. 10. – № 1. – С. 67–74. https://doi.org/10.17816/uroved10167-74

Поступила: 14.01.2020 Одобрена: 20.02.2020 Принята к печати: 19.03.2020

В статье приведен обзор современных данных, посвященный фармакологическим и патогенетическим основам применения селективных ингибиторов фосфодиэстеразы 5-го типа у пациентов с симптомами нижних мочевых путей. Подробно рассмотрены механизмы терапевтического действия этих препаратов при различных дисфункциях мочевых путей, ведущим из которых является улучшение кровообращение и уменьшение ишемии тазовых органов.

Ключевые слова: ингибиторы фосфодиэстеразы 5-го типа; дисфункции нижних мочевых путей; ишемия тазовых органов; тадалафил.

Phosphodiesterase type 5 inhibitors (PDE5Is) have demonstrated efficacy, improved the course, and delayed the progression of endothelial dysfunction. In urological practice, PDE5Is are widely used in the treatment of erectile dysfunction (ED). Furthermore, given the variety of physiological and clinical effects of PDE5Is, the search for new areas of their application continues. PDE5Is might have potential use in the treatment of lower urinary tract dysfunction.

For the first time, new possibilities for the use of PDE5Is were observed when there was an improvement in the urination of patients treated for ED. The first report on this subject was published in 2002 [1] and generated intensive investigation in this area of research. Epidemiological studies confirmed a close relationship between ED and the lower urinary tract symptoms (LUTS). The incidence of LUTS was 72.2% in men with ED, but only 37.7% in men without ED [2]. Similar results were obtained in Russian investigations after interviewing 1225 men aged 22–70 years old [3]. Further studies showed that ED and LUTS had common risk factors along with a high incidence. One of these risk factors mentioned above is metabolic syndrome that clinically presents as diabetes, hypertension, and obesity [4–6].

Most scientists consider pelvic ischemia as a leading pathogenetic factor for pelvic dysfunction. It is also true for both LUTS and ED. Four main general

pathophysiological mechanisms underlie their development: deficiencies in the production of nitric oxide (NO) in the pelvic organs, increased sympathetic activity, increased Rho-kinase activity, and the presence of atherosclerosis of the vessels of the pelvis [7, 8].

1. Deficiencies in the production of NO. The role of NO in providing erectile function is well known. The endothelial isoform of NO synthase in vascular smooth muscle cells activates guanylate cyclase, which leads to an increase in the production of cyclic guanosine monophosphate (cGMP) and, through a cascade of reactions, causes a decrease in intracellular calcium levels and relaxation of cavernous myocytes. Thus, a decrease in NO production is accompanied by impaired erectile function. A deficiency in NO in the urinary tract causes an increase in bladder and urethra smooth muscle tone, as well as an increase in their afferent activity [9, 10]. This is manifested by symptoms of bladder overactivity.

2. Increased sympathetic activity. Experimental and clinical studies showed that lower urinary tract dysfunction and ED were associated with hypertension and closely related to increased sympathetic activity [11, 12]. Hypertension, as well as hyperglycemia, obesity, and hyperlipidemia, are components of the metabolic syndrome, whose relationship with ED and LUTS has been proven by numerous studies [4, 5].

3. Increased Rho-kinase activity. Rho-kinase provides Ca^{2+}-independent smooth muscle cell contraction [13]. The Rho-kinase signaling pathway in endothelial cells leads to decreased activity of NO synthase thus preventing smooth muscle relaxation and promoting the development of ED and LUTS [14]. Increased Rho-kinase activity is reported in patients with diabetes and hypertension [15]. In this regard, an increased Rho-kinase activity is considered as one of the connecting mechanisms between ED and LUTS [16].

4. Atherosclerosis of the vessels of the pelvis. Atherosclerotic vascular disease causes blood circulation impairment and ischemia of pelvic organs and promotes the development of ED and LUTS [17]. Atherosclerotic disease of bladder vessels has been shown experimentally to be accompanied by a decrease in elasticity and expansibility of the bladder wall [18]. Doppler ultrasonography detected a lower cystometric capacity and a higher frequency of urination in cases of more severe vessel atherosclerosis [19]. For pelvic ischemia, bladder filling is associated with a decrease in hemodynamic parameters, and reperfusion after voiding may cause oxidative cell damage. Especially significant reperfusion injuries are pronounced in patients with atherosclerosis of the intravesical vessels [20].

Thus, an impairment of blood flow in the pelvis leading to lower urinary tract ischemia is considered a main pathogenetic factor for lower urinary tract dysfunction. Pelvic ischemia, along with infravesical obstruction and neurological diseases, is proved to be an independent risk factor for bladder overactivity which is one of the components of LUTS [21–23]. Bladder overactivity is a widespread condition that significantly reduces the quality of life of patients [24, 25]. The microcirculation in the bladder wall was studied in patients with bladder overactivity in the urology clinic of Academician I.P. Pavlov First Saint Petersburg State Medical University [26, 27]. The study showed that the severity of microcirculation impairment was correlated with the severity of the symptoms of the disease. Moreover, the degree of arterial blood flow impairment was associated with the severity of urgency, whereas the degree of venous and capillary blood flow impairment was associated with the frequency of urination. The severity of microcirculation impairment in the bladder wall depended on the degree of pelvic sensation and correlated with hypertension, ischemic heart disease, and chronic constipation. The obtained data led to speculation about the drugs that improved the microcirculation in the bladder wall in patients with bladder overactivity [26, 27].

Kershen et al. [28] showed that during bladder filling, the circulation in the bladder worsened, this was related to compression of the intradetrusor vessels, and after voiding, the circulation increased. Acute urinary retention with mechanical compression of the intramural vessels due to increased infravesical pressure causes persistent vasospasm and detrusor ischemia that subsequently leads to bladder dysfunction [29]. An experimental study performed by Vince et al. [30] confirmed that with an increase in intravesicular pressure during the filling phase, a decrease in bladder perfusion occurred. Involuntary bladder contractions because of detrusor overactivity as well as increased intravesicular pressure because of infravesical obstruction and reduced expansibility of the bladder wall because of fibrosis may lead to a blood flow impairment in the bladder wall. With morphological changes in the detrusor associated with ischemia, damage to intramural nerves occurs, which leads to detrusor

denervation, and worsening of bladder dysfunction. Thus, ischemia of the bladder wall is a main pathogenetic mechanism primarily for the bladder overactivity. Then, morphological changes and detrusor decompensation increase and proceed to underactivity. A similar sequence of events was identified earlier in the study of changes in the structure and function of the urinary tract in patients with diabetes complicated by diabetic cystopathy [31–33].

Since ED and LUTS have common pathogenetic mechanisms, the expectations that the treatment methods should also be similar are justifiable. In this regard, the use of PDE5Is fully fits into this concept. The main therapeutic mechanisms of the efficacy of PDE5Is for LUTS are smooth muscle relaxation of the detrusor and urethra and improvement in lower urinary tract circulation. Both effects are due to the therapeutic action of PDE5Is. These drugs inhibit PDE5 that is found in smooth muscle cells of the bladder, urethra, prostate, and vascular wall. PDE5 promotes the conversion of cGMP back to guanosine triphosphate that leads to a decrease in protein kinase G activity, the arrest of NO-dependent signaling, an increase in intracellular calcium, a decrease in potassium concentration, the phosphorylation of actin and myosin, and results in the constriction of urinary tract smooth muscle cells and vasoconstriction [34]. Thus, by increasing the cGMP level in smooth muscle cells, PDE5Is decrease the tone in the lower urinary tract and promote intramural vasodilation, both of which improve blood circulation in the pelvic organs [35, 36]. In experiments, PDE5Is were shown to inhibit Rho-kinase activity, which promoted an improvement in ischemia of the bladder wall [37]. Another mechanism of blood perfusion in the bladder wall is an improvement of blood flow in the vesicular artery. It was established that this artery is characterized by high activity of PDE5, which can be inhibited by tadalafil [36]. An important aspect of the therapeutic action of PDE5Is is the capability to modulate a sensory function of the bladder. A study showed that PDE5Is decreased the mechanosensitive afferent activity of both Aδ- and C-fibers, thereby decreasing bladder sensitivity, an effect that is important for the treatment of patients with overactive bladder [38].

Thus, PDE5Is for the treatment of lower urinary tract dysfunction seem to be pharmacologically and pathogenetically reasonable [10, 21]. Currently, several forms of PDE are known, some of them hydrolase predominately cyclic adenosine monophosphate, others – cGMP. Messenger-RNAs of PDE type 1A, 1B, 2A, 4A, 4B, 5A, 7A, 8A, and 9A are found in bladder tissue. Most of them inhibit the hydrolysis of cGMP [39]. To date, PDE5Is are the most widely used in clinical practice. Using immunohistochemical studies and by evaluating the expression of mRNA with a quantitative polymerase chain reaction, PDE5 was found in the muscle fibers and blood vessels in the bladder, urethra, and prostate gland. The highest concentration of PDE5 was detected in the bladder, and the lowest was in the prostate [40].

The efficacy of PDE5Is was confirmed by a substantial number of experimental and clinical studies. In an experimental study, the capability of PDE5Is to decrease the contractility and afferent activity of the bladder was shown in animals with neurogenic bladder overactivity associated with spinal cord injury [41]. The evidence demonstrating the ability of PDE5Is to improve bladder circulation was also experimentally obtained [42].

Clinical trials proved the efficacy of PDE5Is in the treatment of LUTS either alone or in combination with other drugs [43–46]. For example, improvement in symptoms is observed in week 1 of therapy with tadalafil at a dose of 5 mg per day with a statistically significant decrease in the total international prostate symptom score (IPSS) by 22%–37% [45]. However, despite the significant improvement in IPSS and IIEF (international index of erectile function), PDE5Is had no significant effect on the maximum urinary flow rate compared with placebo [46–48]. An important direction for the clinical application of PDE5Is is their use in combination with other drugs. A meta-analysis of five randomized clinical trials (two studies of tadalafil 20 mg, two studies of sildenafil 25 mg, and one of vardenafil 20 mg) showed that the combined therapy significantly improved scores on the IPSS (–1.8) and IIEF (+3.6), and increased the maximum urinary flow (+1.5 ml/sec) compared to alpha-blocker monotherapy [49].

Sivkov et al. [50] reported results of the study, where the PDE5I vardenafil (20 mg per day) was compared with M-anticholinergic medication solifenacin (5 mg per day) in men with bladder overactivity and ED. The duration of therapy was eight weeks. All patients noted an improvement. In four out of 26 patients in the vardenafil group, symptoms of bladder overactivity resolved completely. There was a positive dynamic in urodynamic parameters in this group. After treatment, an infused mean volume at which the onset of

the first involuntary detrusor contraction (IDC) occurred was increased significantly from 93.9 ± 14.4 to 146.4 ± 13 cm H_2O. The number of IDCs decreased from 2.5 ± 1.1 to 1.9 ± 0.9 cm H_2O. The range of maximum IDCs decreased from 21.1 ± 10 to 15.3 ± 9.4 cm H_2O, and the maximum cystometric capacity increased from 150.2 ± 31.5 to 224.7 ± 40.1 ml. In the solifenacin group, all patients also reported an improvement regarding urinary frequency, urgent urination, and the number of episodes of urge urinary incontinence. The authors concluded that PDE5Is were appropriate as both monotherapy and combined therapy in patients with bladder overactivity [50].

In patients with benign prostatic hyperplasia, PDE5I is one of the pathogenetic methods of treatment. PDE5Is have the following main mechanisms of therapeutic action in men with LUTS associated with benign prostatic hyperplasia: decrease in the muscular tone of the prostate and bladder, decrease of prostate cell proliferation, a decrease of inflammation in the prostate, and inhibition of bladder afferent activity [51, 52].

PDE5Is seem to be pathogenetically reasonable for the treatment of patients with underactive bladder. This condition is manifested by voiding difficulty, absence or significant decrease of urinate desire, and an increase in postvoid residual urine volume. Occasionally, there may be no urination [53]. An urodynamic study revealed decreased detrusor contractility and bladder sensitivity. The reasons for bladder underactivity are variable. Most often, it develops as a complication of neurological diseases (peripheral neuropathies, lumbosacral spinal cord injuries) or as a result of decompensation of the bladder in patients with infravesical obstruction, or because of diseases that directly lead to damage to the bladder vessels, such as diabetes. In addition, regardless of the reason, ischemia of the bladder wall plays an important, and in some cases, a crucial role in the development and progression of bladder underactivity. Thus, hypoxia of the bladder wall is accompanied by the loss of nerve endings (bladder denervation), a decrease in smooth muscle cells, and the proliferation of collagen fibers that frequently render the condition permanent [53, 54].

A special form of bladder dysfunction is distinguished – detrusor overactivity with impaired contractility. Several researchers consider it a transitional state from hyperactivity to underactivity of the detrusor [55]. This condition is manifested by symptoms of underactive bladder (frequent urination, urgent urination, and urge urinary incontinence). In addition, there is urinary difficulty and an increase in postvoid residual urine volume. This means that in the voiding phase, the detrusor does not perform its function in the full range. Such a condition was studied in the experiment and was described for neurologic diseases, bladder outlet obstruction, and diabetes [55–57]. Further progression of this condition leads to "pure" detrusor underactivity.

Gotoh et al. [58] studied the effect of tadalafil on bladder perfusion in an experimental model of diabetic cystopathy with detrusor underactivity. Animals received tadalafil at a dose of 2 mg/kg per day for seven days. The treatment with PDE5Is promoted an increase in parameters specific for microcirculation in the bladder wall and suggested that PDE5Is might improve bladder perfusion [58]. Another study in an experimental model of neurogenic detrusor underactivity showed that an improvement in bladder perfusion promoted an increase in detrusor contractility, and a decrease in bladder capacity and postvoid residual urine volume [59].

Improvement in bladder voiding for detrusor underactivity is the main goal of therapy. This goal can be achieved either by increasing the contractile capability of the detrusor, or by reducing the urethral resistance. Since the relaxation of smooth myocytes of the bladder outlet area is mediated by nitric oxide, PDE5Is in such patients can also have a therapeutic effect. In a recent study, this concept was proved experimentally [60]. In a model of neurogenic detrusor underactivity with detrusor sphincter dyssynergia, tadalafil was associated with a significant decrease in postvoid residual urine volume and an increase in voiding efficiency with no increase in detrusor contractility. Thus, the efficacy of the treatment was achieved by the relaxation of the urethra during voiding that led to an increase in voiding efficiency [60].

Thus, in patients with lower urinary tract dysfunction, PDE5Is are pathogenetically reasonable, and studies showed their clinical efficiency. To date, tadalafil is a single PDE5I recommended by the European Association of Urology and approved by the FDA for LUTS treatment. However, there are clinical trials that proved another PDE5Is to be effective for lower urinary tract dysfunction treatment. Currently, besides tadalafil, there are six commercially available oral PDE5Is, including sildenafil, vardenafil, udenafil, and mirodenafil.

REFERENCES

1. Sairam K, Kulinskaya E, McNicholas TA, et al. Sildenafil influences lower urinary tract symptoms. *BJU Int.* 2002;90(9):836-839. https://doi.org/10.1046/j.1464-410x.2002.03040.x.
2. Braun MH, Sommer F, Haupt G, et al. Lower Urinary Tract Symptoms and Erectile Dysfunction: Co-morbidity or Typical "Aging Male" Symptoms? Results of the "Cologne Male Survey". *Eur Urol*. 2003;44(5): 588-594. https://doi.org/ 10.1016/s0302-2838(03)00358-0.
3. Korneyev I.A., Alekseeva T.A., Al-Shukri S.H., et al. Prevalence and risk factors for erectile dysfunction and lower urinary tract symptoms in russian federation men: analysis from a national population-based multicenter study. *Int J Impot Res.* 2016;28(2):74-79. https://doi.org/10.1038/ijir.2016.8.
4. Kok ET, Schouten BW, Bohnen AM, et al. Risk factors for lower urinary tract symptoms suggestive of benign prostatic hyperplasia in a community based population of healthy aging men: The Krimpen Study. *J Urol.* 2009;181(2):710-716. https://doi.org/10.1016/j.juro.2008.10.025.
5. Kim S, Jeong JY, Choi YJ, et al. Association between lower urinary tract symptoms and vascular risk factors in aging men: The Hallym Aging Study. *Korean J Urol.* 2010;51(7):477-482. https://doi.org/10.4111/kju.2010.51.7.477.
6. Корнеев И.А., Алексеева Т.А., Аль-Шукри С.Х., Пушкарь Д.Ю. Симптомы нижних мочевых путей у мужчин Северо-Западного региона Российской Федерации: анализ результатов популяционного исследования // Урологические ведомости. – 2016. – Т. 6. – № 1. – С. 5–9. [Korneyev IA, Alexeeva TA, Al-Shukri SKh, Pushkar DYu. Lower urinary tract symptoms in male population of the Russian Federation North-Western Region: analysis of population study results. *Urologicheskie vedomosti.* 2016;6(1):5-9 (In Russ.)]. https://doi.org/10.17816/uroved615-9.
7. Speakman MJ PDE5 inhibitors in the treatment of LUTS. *Curr Pharm Des.* 2009;15(30):3502-3205. https://doi.org/10.2174/138161209789207051.
8. Mouli S, McVary KT. PDE5 inhibitors for LUTS. *Prostate Cancer Prostatic Dis*. 2009;12(4):316-24. https://doi.org/10.1038/pcan.2009.27.
9. Hedlund P. Nitric oxide/cGMP-mediated effects in the outflow region of the lower urinary tract — is there a basis for pharmacological targeting of cGMP? *World J Urol*. 2005;23(6):362-367. https://doi.org/10.1007/s00345-005-0019-1.
10. Andersson KE. LUTS treatment: future treatment options. *Neurourol Urodyn*. 2007;26(6):934-947. https://doi.org/ 10.1002/nau.20500.
11. McVary KT, Rademaker A, Lloyd GL, Gann P. Autonomic nervous system overactivity in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia. *J Urol*. 2005;174(4 Pt 1): 1327-1433. https://doi.org/10.1097/01.ju.0000173072.73702.64.
12. Кузьмин И.В. Патогенез, клиническое течение и лечение гиперактивности мочевого пузыря: Дис. … докт. мед. наук. – Санкт-Петербург, 2007. [Kuzmin IV. Patogenez, klinicheskoe techenie i lechenie giperaktivnosti mochevogo puzyrja. [dissertation]. Saint Petersburg; 2007. (In Russ.)]. Доступно по http://www.dslib.net/nefrologia/avtoreferat-patogenez-klinicheskoe-techenie-i-lechenie-giperaktivnosti-mochevogo.html. Ссылка активна на 23.02.2020.
13. Somlyo AP, Somlyo AV. Signal transduction by G-proteins, Rho-kinase and protein phosphatase to smooth muscle and non smooth muscle myosin II. *J Physiol.* 2000;522(Pt 2):177-185. https://doi.org/10.1111/j.1469-7793.2000.t01-2-00177.x.
14. Rees RW, Ziessen T, Ralph DJ, et al. Human and rabbit cavernosal smooth muscle cells express Rho-kinase. *Int J Impot Res.* 2002;14(1):1-7. https://doi.org/10.1038/sj.ijir.3900814.
15. Seko T, Ito M, Kureishi Y, et al. Activation of RhoA and inhibition of myosin phosphatase as important components in hypertension in vascular smooth muscle. *Circ Res.* 2003;92(4):411-418. https://doi.org/10.1161/01.RES.0000059987.90200.44.
16. Rajasekaran M, White S, Baquir A, Wilkes N Rho-kinase inhibition improves erectile function in aging male Brown-Norway rats. *J Androl*. 2005;26(20:182-188. https://doi.org/10.1002/j.1939-4640.2005.tb01084.x.
17. Barbosa JA, Muracca E, Nakano É, et al. Interactions between lower urinary tract symptoms and cardiovascular risk factors determine distinct patterns of erectile dysfunction: a latent class analysis. *J Urol*. 2013;190(6):2177-2182. https://doi.org/10.1016/j.juro.2013.05.048.
18. Azadzoi KM, Tarcan T, Siroky MB, Krane RJ Atherosclerosis-induced chronic ischemia causes bladder fibrosis and non-compliance in the rabbit. *J Urol*. 1999;161(5):1626-1635.
19. Takahashi N, Shishido K, Sato Y, et al. The association between severity of atherosclerosis and lower urinary tract function in male patients with lower urinary tract symptoms. *Low Urin Tract Symptoms.* 2012;4(1):9-13. https://doi.org/10.1111/j.1757-5672.2011.00098.x.
20. Kullmann A, Birder LA, Andersson K-E. Translational Research and Functional Changes in Voiding Function in Older Adults. *Clin Geriatr Med*. 2015;31(4):535-548. https://doi.org/10.1016/j.cger.2015.06.001.
21. Thurmond P, Yang J-H, Azadzoi KM. LUTS in pelvic ischemia: a new concept in voiding dysfunction. *Am J Physiol Renal Physiol.* 2016;310(8):F738-F743 https://doi.org/10.1152/ajprenal.00333.2015.
22. Бердичевский Б.А., Бердичевский В.Б. Ишемия детрузора. Клинические эффекты // Урология. – 2019. – № 5. – С. 132–135. [Berdichevsky BA, Berdichevsky VB Detrusor ischemia. Clinical effects. *Urologiia.* 2019;(5):132-135. (In Russ.)]. https://doi.org/10.18565/urology.2019.5.132-135.
23. Аляев Ю.Г., Есилевский Ю.М., Шмидт Т.Е. и др. Изменения кровообращения в пузырно-уретральном сегменте у мужчин с нейрогенными и ненейрогенными симптомами нижних мо-

чевыводящих путей // Урология. – 2016. – № 6. – С. 17–21. [Alayev YuG, Esilevskiy YuM, Shmidt TE, et al. Alterations in blood circulation of vesicourethral segment in men with neurogenic and non-neurogenic lower urinary tract symptoms. *Urologiia*. 2016;(6):17-21 (In Russ.)]

24. Аль-Шукри С.Х., Кузьмин И.В. Качество жизни больных с гиперактивностью мочевого пузыря // Урологические ведомости. – 2011. – Т. 1. – № 1. – С. 21–26. [Al-Shukri SKh, Kuzmin IV. Quality of life in patients with overactive bladder. *Urologicheskie vedomosti.* 2011;1(1):21-26. (In Russ.)].
25. Кузьмин И.В. Эпидемиологические аспекты гиперактивного мочевого пузыря и ургентного недержания мочи // Урологические ведомости. – 2015. – Т. 5. – № 3. – С. 30–34. [Kuzmin IV. Epidemiological aspects of overactive bladder and urge urinary incontinence. *Urologicheskie vedomosti.* 2015;5(3):30-34. (In Russ.)]. https://doi.org/10.17816/uroved5330-34.
26. Аль-Шукри С.Х., Кузьмин И.В., Амдий Р.Э., и др. Состояние микроциркуляции в стенке мочевого пузыря и клинические проявления гиперактивности мочевого пузыря у женщин // Экспериментальная и клиническая урология. – 2010. – № 2. – С. 52–55. [Al-Shukri SKh, Kuz'min IV, Amdiy RE, et al. Microcirculation in urinary bladder wall and clinical symptoms of overactive bladder in women. *Experimental and Clinical Urology*. 2010;(2): 52-55 (In Russ.)].
27. Аль-Шукри С.Х., Кузьмин И.В., Слесаревская М.Н., Шабудина Н.О. Внутрипузырная ультразвуковая допплерография в оценке состояния кровотока в стенке мочевого пузыря у женщин с ирритативными симптомами // Регионарное кровообращение и микроциркуляция. – 2014. – Т. 13. – № 1(49). – С. 48–54. [Al-Shukri S, Kuzmin I, Slesarevskaya M, Shabudina N. Intravesical Ultrawave Doppler in assessing blood flow in the bladder wall in women with irritative symptoms. *Regional blood circulation and microcirculation.* 2014;13(1 49): 48-54 (In Russ.)]. https://doi.org/10.24884/1682-6655-2014-13-1-48-54.
28. Kershen RT, Azadzoi KM, Siroky MB. Blood flow, pressure and compliance in the male human bladder. *J Urol.* 2002;168(1): 121-125.
29. Кирпатовский В.И., Плотников Е.Ю., Мудрая И.С. и др. Ишемия мочевого пузыря как причина его дисфункции после острой задержки мочи // Экспериментальная и клиническая урология. – 2012. – № 3. – С. 9–13. [Kirpatovskiy VI, Plotnikov EYu, Mudraya IS, et al. Ischemia of the bladder, as the cause of its dysfunction after acute urinary retention. *Experimental and Clinical Urology*. 2012;(3):9-13 (In Russ.)].
30. Vince R, Tracey A, Deebel NA, et al. Effects of vesical and perfusion pressure on perfusate flow, and flow on vesical pressure, in the isolated perfused working pig bladder reveal a potential mechanism for the regulation of detrusor compliance. *Neurourol Urodyn.* 2017;37(2):642-649. https://doi.org/ 10.1002/nau.23362.
31. Кузьмин И.В., Шабудина Н.О. Патогенетические основы развития диабетической цистопатии // Экспериментальная и клиническая урология. – 2014. – № 4. – С. 92–99. [Kuzmin IV, Shabudina NO Pathogenetic basis development of diabetic cystopathy. *Experimental and Clinical Urology*. 2014;(4):92-99 (In Russ.)].
32. Кузьмин И.В., Шабудина Н.О., Аль-Шукри А.С. Симптоматика и клиническое течение цистопатии у больных сахарным диабетом 2 типа // Сахарный диабет. – 2013. – Т. 16. – № 2. – С. 73–76. [Kuzmin IV, Shabudina NO, Al-Shukri AS. Semiology and clinical development of cystopathy in patients with type 2 diabetes mellitus. *Diabetes mellitus*. 2013;16(2):73-76 (In Russ.)]. https://doi.org/10.14341/2072-0351-3759.
33. Аль-Шукри С.Х., Кузьмин И.В., Шабудина Н.О. Дисфункции нижних мочевых путей у больных сахарным диабетом // Уральский медицинский журнал. – 2012. – № 3(95). – С. 114–119. [Al-Shukri SH, Kuzmin IV, Shabudina NO. Lower urinary tract dysfunctions in patients with diabetes mellitus. *Ural Medical Journal.* 2012;(3):114-119. (In Russ.)].
34. Rybalkin SD, Yan C, Bornfeldt KE, Beavo JA. Cyclic GMP phosphodiesterases and regulation of smooth muscle function. *Circ Res.* 2003;93(4):280-291. https://doi.org/10.1161/01.RES.0000087541.15600.2B.
35. Andersson KE, de Groat WC, McVary KT, et al. Tadalafil for the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: pathophysiology and mechanism(s) of action. *Neurourol Urodyn*. 2011;30(3):292-301. https://doi.org/10.1002/nau.20999.
36. Cellek S, Cameron NE, Cotter MA, et al. Microvascular dysfunction and efficacy of PDE5 inhibitors in BPH-LUTS. *Nat Rev Urol.* 2014;11(4):231-241. https://doi.org/10.1038/nrurol.2014.53.
37. Morelli A, Filippi S, Sandner P, et al. Vardenafil modulates bladder contractility through cGMP-mediated inhibition of RhoA/Rho kinase signaling pathway in spontaneously hypertensive rats. *J Sex Med.* 2009;6(6):1594-1608. https://doi.org/10.1111/j.1743-6109.2009.01249.x.
38. Giuliano F, Ückert S, Maggi M, et al. The mechanism of action of phosphodiesterase type 5 inhibitors in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia. *Eur Urol.* 2013;63(3):506-516. https://doi.org/10.1016/j.eururo.2012.09.006.
39. Uckert S, Hedlund P, Andersson KE, et al. Update on phosphodiesterase (PDE) isoenzymes as pharmacologic targets in urology: present and future. *Eur Urol.* 2006;50(6):1194-1207. https://doi.org/ 10.1016/j.eururo.2006.05.025.
40. Fibbi B, Morelli A, Vignozzi L, et al. Characterization of phosphodiesterase type 5 expression and functional activity in the human male lower urinary tract. *J Sex Med.* 2010;7 (1 Pt 1):59-69. https://doi.org/10.1111/j.1743-6109.2009.01511.x.
41. Behr-Roussel D, Oger S, Caisey S, et al. Vardenafil decreases bladder afferent nerve activity in unanesthetized, decerebrate, spi-

nal cord-injured rats. *Eur Urol.* 2010;59(2):272-279. https://doi.org/10.1016/j.eururo.2010.10.03.

42. Choi H, Bae JH, Shim JS, et al. Mirodenafil prevents bladder dysfunction induced by chronic bladder ischemia in rats. *Int Neurourol J*. 2015;19(1):19-26. https://doi.org/10.5213/inj.2015.19.1.19.
43. Porst H, Kim ED, Casabe AR, et al. Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial. *Eur Urol*. 2011;60(5):1105-1113. https://doi.org/10.1016/j.eururo.2011.08.005.
44. Калинина С.Н., Бурлака О.О., Александров М.С., Выдрин П.С. Диагностика и лечение симптомов нижних мочевых путей и эректильной дисфункции у больных доброкачественной гиперплазией предстательной железы // Урологические ведомости. – 2018. – Т. 8. – № 1. – С. 26–33. [Kalinina SN, Burlaka OO, Aleksandrov MS, Vydryn PS Diagnosis and treatment of lower urinary tract symptoms and erectile dysfunction in patients with benign prostate hyperplasia. *Urologicheskie vedomosti.* 2018;8(1):26-33 (In Russ.)]. 10.17816/uroved8126-33.
45. Oelke M, Giuliano F, Mirone V, et al. Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. *Eur Urol.* 2012;61(5): 917-925. https://doi.org/10.1016/j.eururo.2012.01.013.
46. Сивков А.В., Кешишев Н.Г., Ковченко Г.А. Влияние ингибиторов фосфодиэстеразы 5-го типа на симптомы нижних мочевых путей и эректильную функцию у больных ДГПЖ // Экспериментальная и клиническая урология. – 2010. – № 4. – С. 44–49. [Sivkov AV, Keshishev NG, Kovchenko GA. Influence of Phosphodiesterase Type 5 Inhibitors on Lower Urinary Tract Symptoms and Erectile function in Patients with BPH. *Experimental and Clinical Urology.* 2010;(4):44-49 (In Russ.)]
47. Камалов А.А., Низов А.Н. Эффективность ингибиторов фосфодиэстеразы 5-го типа в терапии симптомов нижних мочевыводящих путей у пациентов с доброкачественной гиперплазией предстательной железы и сочетанной эректильной дисфункцией // Урология. – 2019. – № 4. – С. 130–134. [Kamalov AA, Nizov AN. Efficiency of phosphodiesterase-5 inhibitors for treatment of lower urinary tract symptoms in patients with benign prostatic hyperplasia and concomitant erectile dysfunction. *Urologiia.* 2019;(4):130-134. (In Russ.)]. https://doi.org/10.18565/urology.2019.4.130-134.
48. Wang Y, Bao Y, Liu J, et al. Tadalafil 5 mg Once Daily Improves Lower Urinary Tract Symptoms and Erectile Dysfunction: A Systematic Review and Meta-analysis. *Low Urin Tract Symptoms.* 2018;10(1):84-92. https://doi.org/10.1111/luts.12144.
49. Gacci, M, Corona G, Salvi M, et al. A Systematic Review and Meta-analysis on the Use of Phosphodiesterase 5 Inhibitors Flone or in Combination with α-Blockers for Lower Urinary Tract Symptoms Due to Benign Prostatic Hyperplasia. *Eur Urol*. 2012;61(5):994-1003. https://doi.org/10.1016/j.eururo.2012.02.033.
50. Сивков А.В., Ромих В.В., Коршунова Е.С., Коршунов М.Н. Применение ингибиторов фосфодиэстеразы 5 типа у пациентов с гиперактивным мочевым пузырем // Экспериментальная и клиническая урология. – 2010. – № 4. – С. 54–59. [Sivkov AV, Romih VV, Korshunova ES, Korshunov MN. Type 5 Phosphodiesterase Inhibitors in Treatment of Patients with Hyperactive Bladder. *Experimental and Clinical Urology*. 2010;(4):54-59 (In Russ.)]
51. Васильев А.О., Говоров А.В., Касян Г.Р., Пушкарь Д.Ю. Доброкачественная гиперплазия предстательной железы: возможность применения ингибиторов фосфодиэстеразы 5-го типа // Медицинский Совет. – 2016. – № 19. – С. 109–113. [Vasiliev AO, Govorov AV, Kasyan GR, Pushkar DYu Benign prostatic hyperplasia: a possibility to use type 5 phosphoesterase inhibitors. *Meditsinskiy sovet = Medical Council*. 2016;(19):109-113 (In Russ)]. https://doi.org/10.21518/2079-701X-2016-19-109-113.
52. Vignozzi L, Gacci M, Cellai I, et al. PDE5 inhibitors blunt inflammation in human BPH: A potential mechanism of action for PDE5 inhibitors in LUTS. *Prostate*. 2013;73(13): 1391-1402. https://doi.org/ 10.1002/pros.22686.
53. Andersson KE. The many faces of impaired bladder emptying. *Curr Opin Urol*. 2014;24(4):363-369. https://doi.org/ 10.1097/MOU.0000000000000059.
54. Osman NI, Chapple CR, Abrams P, et al. Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis. *Eur Urol.* 2014;65(2):389-398. https://doi.org/10.1016/j.eururo.2013.10.015.
55. Chancellor MB. The overactive bladder progression to underactive bladder hypothesis. *Int Urol Nephrol.* 2014;46(Suppl. 1):S23-27. https://doi.org/10.1007/s11255-014-0778-y.
56. Аль-Шукри С.Х., Амдий Р.Э., Кузьмин И.В. Снижение сократимости мочевого пузыря у больных доброкачественной гиперплазией предстательной железы // Урологические ведомости. – 2011. – Т. 1. – № 1. – С. 3–8. [Al-Shukri SKh, Amdiy RE, Kuzmin IV. Decrease of urinary bladder contractility in patients with benign prostate hyperplasia. *Urologicheskie vedomosti.* 2011;1(1):3-8 (In Russ.)].
57. Аль-Шукри С.Х., Кузьмин И.В., Шабудина Н.О. Состояние уродинамики нижних мочевых путей у больных с диабетической цистопатией // Урологические ведомости. – 2012. – Т. 2. – № 4. – С. 3–7. [Al-Shukri SKh, Kuzmin IV, Shabudina NO. Urodynamics of lower urinary tract in patients with diabetic cystopathy. *Urologicheskie vedomosti.* 2012;2(4):3-7. (In Russ.)]. https://doi.org/10.17816/uroved243-7.
58. Gotoh D., Torimoto K, Tatsumi Y, et al. Tadalafil, a phosphodiesterase type 5 inhibitor, improves bladder blood supply and restores the initial phase of lower urinary tract dysfunction in diabetic rats. *Neurourol Urodyn.* 2018;37(2):666-672. https://doi.org/ 10.1111/luts.12272.

59. Sekido N, Kida J, Mashimo H, Wakamatsu D, et al. Promising effects of a novel EP2 and EP3 receptor dual agonist, ONO-8055, on neurogenic underactive bladder in a rat lumbar canal stenosis model. *J Urol*. 2016;196(2):609-616. https://doi.org/10.1016/j.juro.2016.02.064.

60. Takaoka EI, Kurobe M, Suzuki T, et al. Urethral dysfunction and therapeutic effects of a PDE5 inhibitor (tadalafil) in a rat model of detrusor underactivity induced by pelvic nerve crush injury. *Neurourol Urodyn*. 2020;39(3):916-925. https://doi.org/10.1002/nau.24310.

Information about the authors:

Igor V. Kuzmin – Doctor of Medical Science, Professor, Urology Department. Academician I.P. Pavlov First Saint Petersburg State Medical University, Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: kuzminigor@mail.ru.

Abdul Kh. Ajub – Postgraduate, Department of Urology. Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: hammad.315@yandex.ru.

Margarita N. Slesarevskaya – Candidate of Medical Science, Senior Research Fellow, Urology Research Center. Academician I.P. Pavlov First Saint Petersburg State Medical University of the Ministry of Healthcare of the Russian Federation, Saint Petersburg, Russia. E-mail: mns-1971@yandex.ru.

Сведения об авторах:

Игорь Валентинович Кузьмин — д-р мед. наук, профессор кафедры урологии. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава России, Санкт-Петербург. E-mail: kuzminigor@mail.ru.

Абдул Хамидович Аюб — аспирант кафедры урологии. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава России, Санкт-Петербург. E-mail: hammad.315@yandex.ru.

Маргарита Николаевна Слесаревская — канд. мед. наук, старший научный сотрудник Научно-исследовательского центра урологии. ФГБОУ ВО ПСПбГМУ им. акад. И.П. Павлова Минздрава России, Санкт-Петербург. E-mail: mns-1971@yandex.ru.