DOI: https://doi.org/10.17816/uroved626639
Review Article

Effectiveness of Wobenzym in combined therapy of chronic bacterial prostatitis. Results of systematic review and meta-analysis

Yuriy A. Kupriyanov [1–3], Andrey V. Zaitsev [1], Alexander N. Bernikov [1], Lyubov A. Khodyreva [2], Dmitry Yu. Pushkar [1, 3]

[1] Russian University of Medicine, Moscow, Russia;
[2] Research Institute of Health Care Organization and Medical Management of the Moscow City Health Department, Moscow, Russia;
[3] S.P. Botkin City Clinical Hospital, Moscow, Russia

ABSTRACT

A systematic review and meta-analysis of research data on the effectiveness of the drug Wobenzym in the treatment of chronic bacterial prostatitis was performed. The aim of this study — to evaluate the effectiveness of Wobenzym in the complex therapy of chronic bacterial prostatitis. The analysis included randomized and non-randomized controlled studies of the effectiveness of Wobenzim in the complex therapy of chronic bacterial prostatitis. The search was carried out in the databases CENTRAL, PubMed, ICTRP, eLibrary, ClinicalTrials.gov., Google Scholar, CyberLeninka, search engines. The meta-analysis was conducted using the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions. Statistical heterogeneity was assessed using the Cochran test and visually when constructing forest plots. A random effects model and a fixed effect model were used. Works published over the entire period were analyzed, 712 publications were identified, of which 9 fully met the stated criteria, all studies were non-randomized controlled. The final analysis included the results of 1292 patients. According to the meta-analysis, it was possible to establish the superiority of complex therapy including Wobenzym compared to therapy without Wobenzym in all studied parameters: eradication of the pathogen, decrease in the number of points on the Quality of Life (QoL) scale, an increase in the linear speed of blood flow in the veins and peak systolic blood flow velocity in the arteries of the prostate gland, maximum urine flow rate, reduction in the number of points of the NIH-CPSI "Pain" subscale (difference 5 points) and NIH-CPSI "Quality of Life" subscale. The use of therapy including Wobenzym in patients with chronic prostatitis leads to a greater increase in the number of $CD4^+$, $CD8^+$ lymphocytes, phagocytic activity of lymphocytes, the level of complement CH-100 and immunoglobulins M, G, A. A systematic review/meta-analysis revealed an objective, statistically significant, positive effect of the drug Wobenzym in the complex therapy of patients with chronic bacterial prostatitis, which is associated with its pathogenetic orientation in relation to this group of patients.

Keywords: chronic bacterial prostatitis; Wobenzym; meta-analysis.

To cite this article
Kupriyanov YuA, Zaitsev AV, Bernikov AN, Khodyreva LA, Pushkar DYu. Effectiveness of Wobenzym in combined therapy of chronic bacterial prostatitis. Results of systematic review and meta-analysis. *Urology reports (St. Petersburg)*. 2024;14(1):51–64. DOI: https://doi.org/10.17816/uroved626639

Received: 13.02.2024 **Accepted:** 25.02.2024 **Published:** 29.03.2024

DOI: https://doi.org/10.17816/uroved626639
Обзорная статья

Эффективность препарата Вобэнзим в комбинированной терапии хронического бактериального простатита. Результаты систематического обзора и метаанализа

Ю.А. Куприянов [1–3], А.В. Зайцев [1], А.Н. Берников [1], Л.А. Ходырева [2], Д.Ю. Пушкарь [1, 3]

[1] Российский университет медицины, Москва, Россия;
[2] Научно-исследовательский институт организации здравоохранения и медицинского менеджмента Департамента здравоохранения г. Москвы, Москва, Россия;
[3] Городская клиническая больница им. С.П. Боткина Департамента здравоохранения г. Москвы, Москва, Россия

АННОТАЦИЯ

Представлен систематический обзор и метаанализ данных исследований по эффективности применения лекарственного препарата Вобэнзим в терапии хронического бактериального простатита. Цель работы — оценить эффективность препарата Вобэнзим в комплексной терапии хронического бактериального простатита. В анализ включены рандомизированные и нерандомизированные контролируемые исследования эффективности препарата в комплексной терапии заболевания. Поиск проводили в базах данных CENTRAL, PubMed, ICTRP, eLibrary, ClinicalTrials.gov., Google Scholar, КиберЛенинка, поисковых систем, с использованием рекомендаций Cochrane Handbook for Systematic Reviews of Interventions. Статистическую гетерогенность оценивали с помощью критерия Кокрана и визуально при построении «forest plots». Использовалась модель случайных эффектов и модель фиксированного эффекта. Были проанализированы работы, опубликованные за все время, выявлены 712 публикаций, из которых 9 полностью соответствовали заявленным критериям, все исследования были нерандомизированными контролируемыми. В окончательный анализ вошли результаты лечения 1292 пациентов. По данным метаанализа удалось установить превосходство комплексной терапии, включающей Вобэнзим, над терапией без данного препарата по всем исследуемым параметрам: эрадикация возбудителя, снижение количества баллов по шкале качества жизни (QoL), увеличение линейной скорости кровотока в венах и пиковой систолической скорости кровотока в артериях предстательной железы, максимальной скорости потока мочи, уменьшение количества баллов подшкалы «Боль» (разница 5 баллов) и количества баллов подшкалы «Качество жизни» опросника NIH-CPSI. Применение терапии, включающей Вобэнзим, у пациентов с хроническим простатитом приводит к большему увеличению числа $CD4^+$- и $CD8^+$-лимфоцитов, фагоцитарной активности лимфоцитов, уровня комплимента CH-100 и иммуноглобуллинов M, G, A. Проведенный систематический обзор и метаанализ выявили объективное статистически достоверное положительное влияние препарата Вобэнзим в комплексной терапии пациентов с хроническим бактериальным простатитом, что связано с его патогенетической направленностью в отношении этой группы пациентов.

Ключевые слова: хронический бактериальный простатит; Вобэнзим; метанализ.

Как цитировать

Куприянов Ю.А., Зайцев А.В., Берников А.Н., Ходырева Л.А., Пушкарь Д.Ю. Эффективность препарата Вобэнзим в комбинированной терапии хронического бактериального простатита. Результаты систематического обзора и метаанализа // Урологические ведомости. 2024. Т. 14. № 1. С. 51–64. DOI: https://doi.org/10.17816/uroved626639

Рукопись получена: 13.02.2024 **Рукопись одобрена:** 25.02.2024 **Опубликована:** 29.03.2024

INTRODUCTION

Chronic prostatitis is very common among young and middle-aged men [1, 2]. The global incidence of chronic prostatitis is 2.2–9.7% [2, 3]. In recent years, the incidence has been steadily growing [4–6]. Chronic inflammation in the prostate is caused by a variety of pathological reactions, including anatomical and physiological characteristics of the prostate, the presence of a pathogen capable of adhesion and biofilm production, microcirculatory disorders, and fibrosis [7, 8].

Exacerbations of chronic bacterial prostatitis (CBP) are characterized by pain, sexual dysfunction, dysuria, and psycho-emotional disorders [9, 10]. Currently, CBP is treated using combination therapy. Antibiotics are first-choice drugs. In 2023, the European Association of Urology (EAU) advocated using fluoroquinolones, despite uropathogens being highly resistant to them. Fluoroquinolones are recommended as first-line drugs for empirical treatment of CBP because of their good pharmacokinetic properties, generally favorable safety profile, and activity against gram-negative bacteria [11]. Pathogenesis-oriented combination therapy with antibiotics, herbal extracts, and alternative therapy drugs is recommended [12, 13]. However, symptoms persist in many patients even after treatment is completed [14], which is frequently associated with the failure to eradicate the CBP pathogen [9], immune disorders, and local inflammation with connective tissue fibrosis in the prostate.

Thus, the prevalence of CPB, recurrent or persistent inflammation, and increasing resistance of uropathogenic flora necessitate the search for drugs that improve therapy outcomes, with the potential for long-term use in combination therapy and subsequent relapse prevention.

To successfully treat CBP patients, drugs targeting individual components or influencing several components of pathogenesis are used as adjuvant/alternative therapy. An example of such drugs is Wobenzym, a combination of highly active plant and animal enzymes. This combination includes pancreatin, papain, bromelain, trypsin, lipase, amylase, chymotrypsin, and rutoside trihydrate. According to the product information, Wobenzym has anti-inflammatory, immunomodulatory, fibrinolytic, antiplatelet, antiedemic, and secondary analgesic effects[1]. Enzyme combinations enhance the effect of antibacterials [15]. Wobenzym has the ability to improve etiotropic drug delivery to the site of infection, increase the accessibility of the carrier cell and pathogen receptors, reduce acidity at the inflammation site, and change the properties of microbial biofilms [16]. Enzymes enhance the phagocytic and cytotoxic activity of immune cells (monocytes/macrophages, natural killer cells, and T cells). The therapeutic effect of Wobenzym stems from its effects on inflammation, immunity, and vascular platelet hemostasis[2] [17]. The efficacy of Wobenzym in the treatment of CBP requires further research.

BACKGROUND

So far, no meta-analyses of the efficacy of Wobenzym in CBP have been published. As a result, crucial questions remain. What impact does it have on pathogen eradication rates? What impact does it have on symptoms and quality of life in CBP patients? What effect does Wobenzym have on blood flow and urine flow rate when added to combination therapy for CBP?

The aim of this study was to assess the efficacy of Wobenzym in combination therapy for CBP.

The review included randomized and non-randomized controlled efficacy studies of Wobenzym in combination therapy for CBP. The study included CBP patients, regardless of age, race, or social class. The study compared combination therapy for CBP with and without Wobenzym. The endpoints were defined as follows.

Primary endpoint:

1. Pathogen eradication rate after treatment.

Secondary endpoints:

1. Changes in the Quality of Life (QoL) score after treatment.

2. Changes in prostate ultrasound findings (peak systolic velocity in arteries, linear blood flow velocity in veins) after treatment.

3. Changes in the maximum urine flow rate after treatment.

4. Changes in the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI) score after treatment (Pain and Quality of Life domains).

5. Changes in immunogram parameters after treatment.

Electronic database search

The search was performed in the following databases: PubMed (https://www.nlm.nih.gov), using the search terms “clinical trial”, “humans”, “Wobenzym”, and “prostatitis”; Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library (https://www.cochranelibrary.com/central), National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), and World Health Organization International Clinical Trials Registry Platform (ICTRP) (https://www.who.int/ictrp/en/), using the search term “Wobenzym”;

[1] Wobenzym Summary of Product Characteristics ЛП-№(002667)-(РГ-RU) dated June 30, 2023. https://grls.minzdrav.gov.ru/InstrImg/2023/07/13/1495064/c9c87bad-c031-41fb-b6eb-1fe76b5d97fd.pdf

[2] Wobenzym Summary of Product Characteristics ЛП-№(002667)-(РГ-RU) dated June 30, 2023. https://grls.minzdrav.gov.ru/InstrImg/2023/07/13/1495064/c9c87bad-c031-41fb-b6eb-1fe76b5d97fd.pdf

Google Scholar (https://scholar.google.ru/), using the search terms “clinical trial”, “Wobenzym”, “prostatitis”, “исследование” (clinical trial), “Вобэнзим” (Wobenzym), and “простатит” (prostatitis); eLibrary.ru (http://elibrary.ru), using the search terms “Вобэнзим” (Wobenzym), and “простатит” (prostatitis); CyberLeninka (http://cyberleninka.ru), using the search terms “clinical trial”, “Wobenzym”, “prostatitis”, “исследование” (clinical trial), “Вобэнзим” (Wobenzym), and “простатит” (prostatitis); Gray Zone (search engine results), using the search terms “clinical trial”, “Wobenzym”, and “prostatitis”, “исследование” (clinical trial), “Вобэнзим” (Wobenzym), and “простатит” (prostatitis).

Study heterogeneity assessment

The degree of heterogeneity was assessed visually, and forest plots were made. A quantitative assessment was also conducted by calculating the chi-square test (threshold: $p < 0.10$), I^2, and τ^2. The following heterogeneity classification for I^2 values was used: 0–25%, no heterogeneity; 25–50%, low; 50–75%, moderate; >75%, high.

Bias assessment

The risk of bias was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins J., 2021) [18] for randomized and non-randomized studies. The assessment was performed according to the Cochrane Collaboration guidelines [19] using a validated questionnaire by O.Yu. Rebrova et al. (2015) [20]. The Robvis tool was used for data visualization [21]. We rated the risk of bias as “low,” “high,” or “unclear” for each study separately and for all studies together. Any disagreements that emerged at any point were settled through discussion.

Data synthesis

Data synthesis was based on a conservative assumption that all authors provided their findings as standard error (*SE*), which were then converted to standard deviation (*SD*) according to the formula $SD = SE \times \sqrt{n}$, where n is the number of patients in the group. The R language and RStudio platform (version R) were used for the analysis.

Data integration and analysis

We used the GRADE approach for data interpretation [22].

Search results

Following the search and screening of eligible studies, 9 of 712 identified articles were included in the analysis (Fig. 1).

None of the studies had a high risk of bias in any domain (Fig. 2).

RESULTS

The review included 9 non-randomized studies in 1,292 CBP patients. The studies were published in the Russian language between 2004 and 2020. Their characteristics are presented in Table 1.

Pathogen eradication rate after treatment

This parameter was provided in the required format in the following articles: Dosta N.I. (2013) [15], Ershov E.V. (2007) [25], Noskov N.Yu. (2004) [27], Tkachuk V.N. (2015) [28], and Tkachuk V.N. (2007) [29] (Table 2).

There was no heterogeneity ($I^2 = 0\%$), $\tau^2 = 0.18$ and 0.005, $p > 0.10$. The 95% confidence interval (CI) of the pooled odds ratio (OR), calculated for both the fixed and random effects models, did not cross 1 (Table 3, Fig. 3).

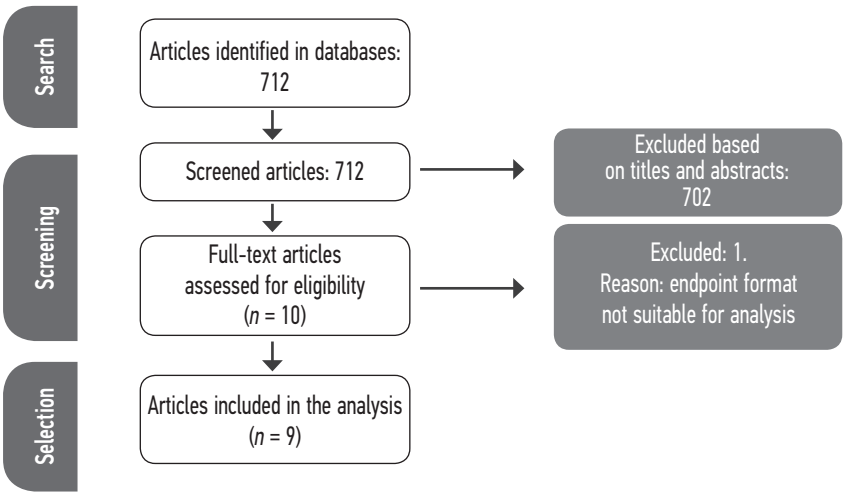

Fig. 1. Block diagram PRISMA [23]
Рис. 1. Блок-схема PRISMA [23]

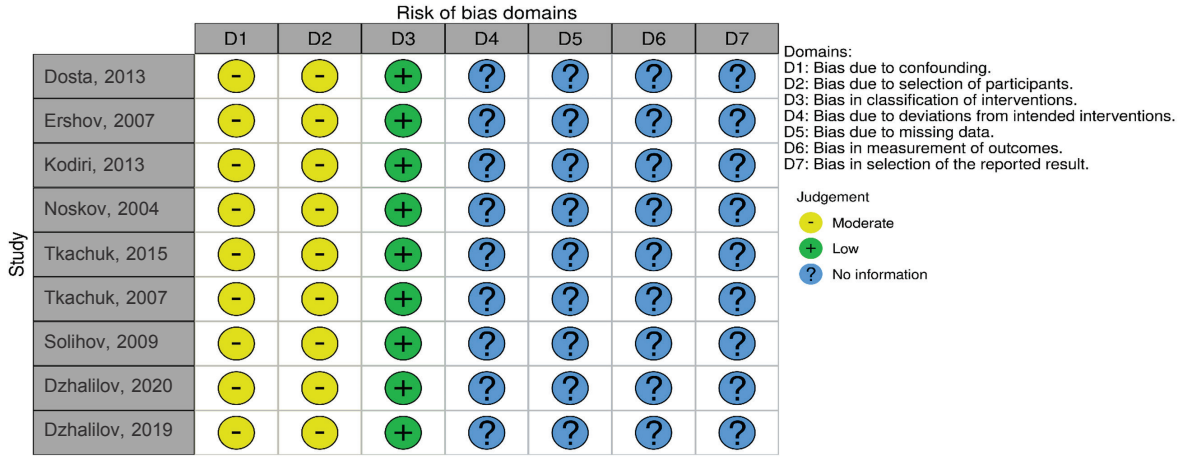

Fig. 2. Assessing the risk of bias across studies. D1 — confounding bias; D2 — selection bias, D3 — intervention classification bias; D4 — intervention bias; D5 — missing data bias; D6 — bias when measuring results; D7 — systematic error in selecting the reported result

Рис. 2. Оценка риска систематической ошибки по исследованиям. D1 — предвзятость из-за смешения; D2 — предвзятость в отборе участников исследования; D3 — предвзятость в классификации вмешательств; D4 — смещение из-за отклонений от запланированных вмешательств; D5 — систематическая ошибка из-за отсутствия данных; D6 — систематическая ошибка при измерении результатов; D7 — систематическая ошибка при выборе сообщаемого результата; Low — низкий; Moderate — умеренный; No information — нет информации

Table 1. Main characteristics of included studies

Таблица 1. Основные характеристики включенных исследований

Author, year	Pathology	Randomization	Subjects, *n*	Mean age	Treatment group		Control group	
					n	therapy	*n*	therapy
Dzhalilov H.N. (2020) [24]	CBP	no	84	67.5	44	Drugs improving prostate microcirculation and hemodynamics, antibiotics, polyoxidonium, Wobenzym	40	Drugs improving rostate microcirculation and hemodynamics, antibiotics
Dosta N.I. (2013) [15]	CBP	no	35	21.0 ± 7.9	20	Antibiotics, Wobenzym	15	Antibiotics
Ershov E.V. (2007) [25]	CBP	no	239	25.6 ± 3.5	66	Antibiotics, Wobenzym	40	Antibiotics
Kodiri T.R. (2013) [26]	CBP	no	68	–	28	Antibiotics, Wobenzym	40	Antibiotics
Noskov N.Yu. (2004) [27]	CBP	no	110	–	70	Antibiotics, Wobenzym	40	Antibiotics
Tkachuk V.N. (2015) [28]	CBP	no	250	28.6 ± 4.5	210	Antibiotics, Wobenzym	40	Antibiotics
Tkachuk V.N. (2007) [29]	CBP	no	237	28.3 ± 2.9	70	Antibiotics, Wobenzym	65	Antibiotics
Solihov D.N. (2009) [30]	CBP	no	135	33.5 ± 4.6	70	Antibiotics, Wobenzym	65	Antibiotics
Dzhalilov H.N. (2019) [31]	CBP	no	134	–	67	Antibiotics, Wobenzym	67	Antibiotics

Thus, therapy with Wobenzym in CBP patients significantly more often results in pathogen eradication compared to therapy without Wobenzym. The OR of the fixed effects model was 11.19 (95% CI 6.42, 19.50; $p = 0.00$); the OR of the random effects model was 11.22 (95% CI 5.75, 21.88; $p = 0.00$).

Changes in the QoL score after treatment with Wobenzym

This parameter was provided in the required format in the following articles: Dosta N.I. (2013) [15], Jalilov Kh.N. (2020) [24], and Jalilov Kh.N. (2019) [31] (Table 4).

Table 2. Results of studies on eradication of uropathogens

Таблица 2. Результаты исследований по эрадикации уропатогенов

Author, year	Treatment group			Control group		
	n	uropathogen isolation rate, %		*n*	uropathogen isolation rate, %	
		before treatment	after treatment		before treatment	after treatment
Dosta N.I. (2013) [15]	20	100	47	15	100	73.0
Ershov E.V. (2007) [25]	66	100	4.5	40	100	37.5
Noskov N.Yu. (2004) [27]	70	100	4.3	40	100	35
Tkachuk V.N. (2015) [28]	210	100	3.8	40	100	44.5
Tkachuk V.N. (2007) [29]	70	100	4.3	65	100	35.3

Table 3. Eradication rates and eradication odds ratios of uropathogens for each study

Таблица 3. Частота эрадикации и отношение шансов эрадикации уропатогенов по каждому исследованию

Study	Treatment group		Control group		OR	95% CI	
	n	events	*n*	events		lower limit	upper limit
Dosta N.I. (2013) [15]	20	11	15	4	3.36	0.79	14.25
Ershov E.V. (2007) [25]	66	63	40	25	12.60	3.35	47.32
Noskov N.Yu. (2004) [27]	70	67	40	26	12.03	3.19	45.32
Tkachuk V.N. (2015) [28]	210	202	40	23	18.66	7.26	48.00
Tkachuk V.N. (2007) [29]	70	67	65	42	12.23	3.46	43.27

Note. OR, odds ratio; CI, confidence interval.

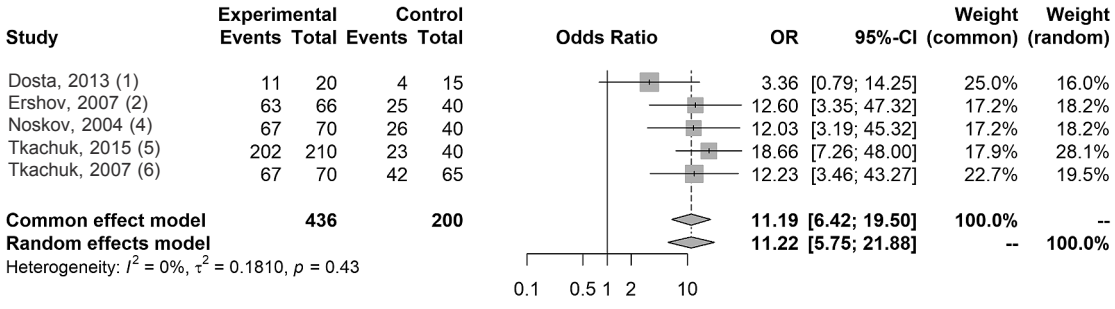

Fig. 3. Meta-analysis of the frequency of eradication of pathogens after therapy including Wobenzym

Рис. 3. Метаанализ частоты эрадикации возбудителей после терапии, включающей Вобэнзим

Heterogeneity was low (I^2 = 32%), τ^2 = 0.17, p > 0.10. The 95% CI of the pooled mean difference for a decrease in the QoL score, calculated for both the fixed and random effects models, did not cross 0, indicating a positive effect of the treatment on quality of life (Fig. 4).

Thus, therapy with Wobenzym in CBP patients significantly decreases the QoL score compared to therapy without Wobenzym, indicating an improvement in quality of life. The mean difference (MD) was –2.02 (95% CI –2.44, –1.59; p = 0.00) in the fixed effects model and –1.82 (95% CI –2.54, –1.11; p = 0.00) in the random effects model.

Changes in the linear blood flow velocity in prostate veins after treatment

This parameter was provided in the required format in the following articles: Ershov E.V. (2007) [25] and Tkachuk V.N. (2015) [28] (Table 5).

Heterogeneity was low (I^2 = 42%), τ^2 = 0.17, p > 0.10. The 95% CI of the pooled mean difference, calculated for both the fixed and random effects models, did not cross 0 (Fig. 5).

Thus, therapy with Wobenzym in CBP patients significantly increases the linear blood flow velocity in prostate veins by more than 1 cm/s compared to therapy without Wobenzym. The mean difference (MD) was 1.07 (95% CI 0.62, 1.51; p = 0.00) in the fixed effects model and 1.20 (95% CI 0.42, 1.68; p = 0.00) in the random effects model.

Changes in the peak systolic velocity in prostate arteries after treatment

This parameter was provided in the required format in the following articles: Ershov E.V. (2007) [25], Tkachuk V.N. (2007) [29], and Tkachuk V.N. (2015) [28] (Table 6).

There was no heterogeneity (I^2 = 0%), τ^2 = 0.06, p > 0.10. The 95% CI of the pooled mean difference, calculated for both the fixed and random effects models, did not cross 0 (Fig. 6).

Thus, therapy with Wobenzym in CBP patients significantly increases the peak systolic velocity in prostate arteries compared to therapy without Wobenzym. The between-group difference was 3.5 cm/s; thus, the peak systolic velocity in patients receiving Wobenzym was approximately 30% higher compared to control.

Table 4. Quality of life indicators on the QoL scale according to research data

Таблица 4. Показатели качества жизни по шкале QoL по данным исследований

Study	Treatment group			Control group			*MD*	95% CI	
	n	*M*	*SD*	*n*	*M*	*SD*		lower limit	upper limit
Dzhalilov H.N. (2019) [31]	44	1.8	1.33	40	4.0	0.89	–2.2	–2.68	–1.72
Dzhalilov H.N. (2020) [24]	51	2.7	2.14	51	4.2	3.57	–1.5	–2.64	–0.36
Dosta N.I. (2013) [15]	20	1.0	3.13	15	2.0	1.55	–1.0	–2.58	0.58

Note. Here and in Tables 5–9: M, mean; SD, standard deviation; MD, mean difference; CI, confidence interval.

Table 5. Indicators of linear blood flow velocity in the veins of the prostate gland according to research data, cm/s

Таблица 5. Показатели линейной скорости кровотока в венах предстательной железы по данным исследований, см/с

Study	Treatment group			Control group			*MD*	95% CI	
	n	*M*	*SD*	*n*	*M*	*SD*		lower limit	upper limit
Ershov E.V. (2007) [25]	66	4.92	1.54	40	3.98	1.01	0.94	0.45	1.43
Tkachuk V.N. (2015) [28]	210	4.91	4.49	40	3.12	3.23	1.79	0.62	2.96

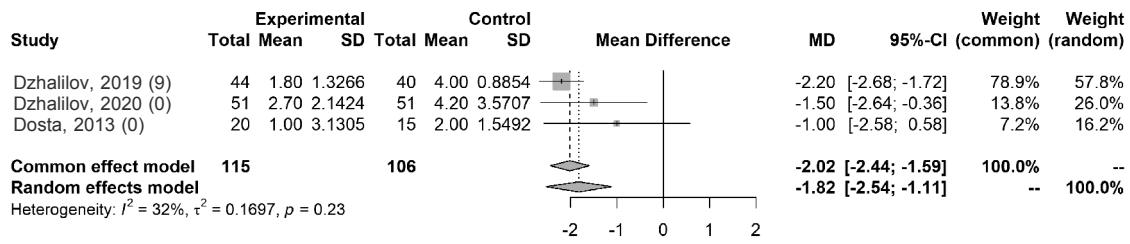

Fig. 4. Meta-analysis of changes in QoL scores after treatment

Рис. 4. Метаанализ изменения баллов по шкале QoL после лечения

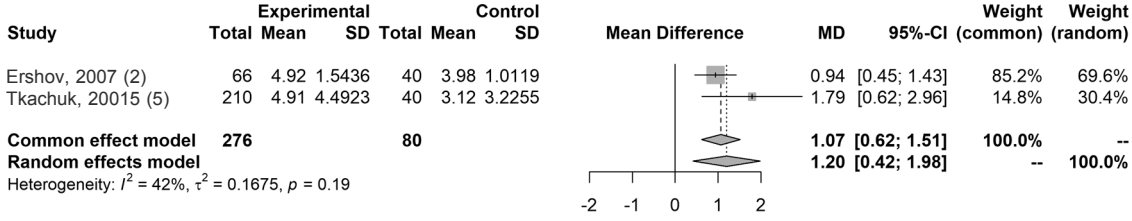

Fig. 5. Meta-analysis of changes in the linear velocity of blood flow in the veins of the prostate gland after treatment

Рис. 5. Метаанализ изменения линейной скорости кровотока в венах предстательной железы после лечения

The mean difference (MD) was 3.48 (95% CI 2.67, 4.29; p = 0.00) in the fixed effects model and 3.48 (95% CI 2.62, 4.34; p = 0.00) in the random effects model.

Changes in the maximum urine flow rate after treatment

This parameter was provided in the required format in the following articles: Kodiri T.R. (2013) [28], Solikhov D.N. (2009) [30], and Jalilov Kh.N. (2019) [31] (Table 7).

There was no heterogeneity (I^2 = 0%), τ^2 = 0.0005, p > 0.10. The 95% CI of the pooled mean difference, calculated for both the fixed and random effects models, did not cross 0 (Fig. 7).

Thus, therapy with Wobenzym in CBP patients significantly increases the maximum urine flow rate compared to therapy without Wobenzym. The mean difference (MD) was 6.01 (95% CI 3.9, 8.11; p = 0.00) in the fixed effects model and 6.01 (95% CI 3.9, 8.11; p = 0.00) in the random effects model.

Changes in the NIH-CPSI Pain domain score after treatment

This parameter was provided in the required format in the following articles: Dosta N.I. (2013) [15] and Tkachuk V.N. (2015) [28] (Table 8).

Heterogeneity was moderate (I^2 = 64%), τ^2 = 4.87, p = 0.10. The 95% CI of the pooled mean difference, calculated for both the fixed and random effects models, did not cross 0 (Fig. 8).

Thus, therapy with Wobenzym in CBP patients significantly decreases the NIH-CPSI Pain domain score compared to therapy without Wobenzym. The between-group difference was 5 points. The mean difference (MD) was

Table 6. Indicators of peak systolic blood flow velocity in the arteries of the prostate gland according to research data, cm/s

Таблица 6. Показатели пиковой систолической скорости кровотока в артериях предстательной железы по данным исследований, см/с

Study	Treatment group			Control group			*MD*	95% CI	
	n	*M*	*SD*	*n*	*M*	*SD*		lower limit	upper limit
Ershov E.V. (2007) [25]	66	13.92	2.84	40	10.62	3.42	3.30	2.04	4.56
Tkachuk V.N. (2007) [29]	70	13.02	3.01	65	10.06	6.77	2.96	1.17	4.75
Tkachuk V.N. (2015) [28]	210	14.02	5.65	40	10.06	3.42	3.96	2.65	5.27

Table 7. Indicators of maximum urine flow rate according to research data, mL/s

Таблица 7. Показатели максимальной скорости потока мочи по данным исследований, мл/с

Study	Treatment group			Control group			*MD*	95% CI	
	n	*M*	*SD*	*n*	*M*	*SD*		lower limit	upper limit
Dzhalilov H.N. (2019) [31]	44	19.0	8.62	40	13.1	7.59	5.9	2.43	9.37
Kodiri T.R. (2013) [28]	28	19.5	6.35	40	13.2	10.75	6.3	2.22	10.38
Solihov D.N. (2009) [30]	70	19.0	10.88	65	13.1	9.67	5.9	2.43	9.37

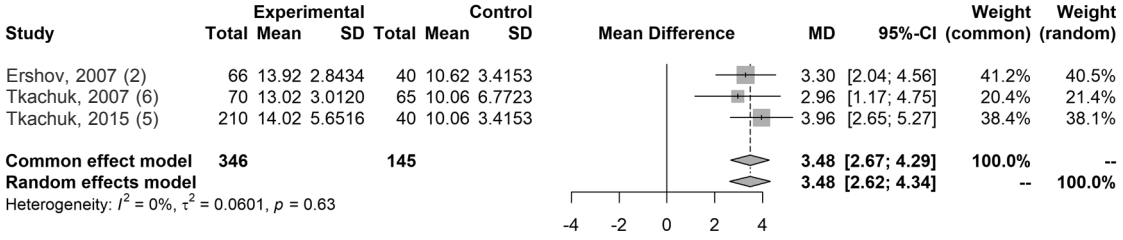

Fig. 6. Meta-analysis of changes in peak systolic blood flow velocity in the prostate arteries after treatment

Рис. 6. Метаанализ изменения пиковой систолической скорости кровотока в артериях предстательной железы после лечения

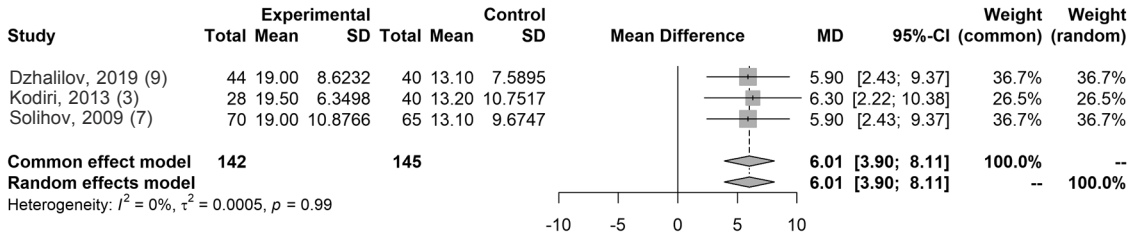

Fig. 7. Meta-analysis of changes in maximum urine flow rate after treatment
Рис. 7. Метаанализ изменения максимальной скорости потока мочи после лечения

–5.17 (95% CI –7.33, –3.0; p = 0.00) in the fixed effects model and –4.60 (95% CI –8.45, –0.76; p = 0.02) in the random effects model.

Changes in the NIH-CPSI Quality of Life domain score after treatment

This parameter was provided in the required format in the following articles: Dosta N.I. (2013) [15] and Tkachuk V.N. (2015) [28] (Table 9).

Heterogeneity was moderate (I^2 = 73%), τ^2 = 1.86, p < 0.10. The 95% CI of the pooled mean difference, calculated for both the fixed and random effects models, did not cross 0 (Fig. 9).

Thus, therapy with Wobenzym in CBP patients significantly decreases the NIH-CPSI Quality of Life domain score compared to therapy without Wobenzym. The between-group difference was 2 points. The mean difference (MD) was –2.61 (95% CI –3.77, –1.45; p = 0.00) in the fixed effects model and –2.32 (95% CI –4.57, –0.08; p = 0.04) in the random effects model.

Changes in immunogram parameters after treatment

This parameter was provided in the required format only in one article: Noskov N.Yu. (2004) [27] (Table 10).

After the treatment, immunogram parameters significantly improved in both groups. However, there was a greater increase in $CD4^+$ T cells, $CD8^+$T cells, lymphocyte activity, CH100, and IgM, IgG, and IgA in the treatment group [29].

The study by Tkachuk V.N. et al. (2015) [28] also provides immunology examination findings. Patients in the treatment group who received combination therapy with Wobenzym showed an improvement in all immunology parameters significantly earlier. Before treatment, CBP

Table 8. NIH-CPSI Pain Subscale Scores according to research data
Таблица 8. Показатели баллов подшкалы «Боль» NIH-CPSI по данным исследований

Study	Treatment group			Control group			*MD*	95% CI	
	n	*M*	*SD*	*n*	*M*	*SD*		lower limit	upper limit
Dosta N.I. (2013) [15]	20	5.9	8.50	15	8.1	3.49	–2.2	–6.32	1.92
Tkachuk V.N. (2015) [28]	210	2.1	7.25	40	8.4	7.59	–6.3	–8.85	–3.75

Table 9. NIH-CPSI Quality of Life Subscale Scores according to research data
Таблица 9. Показатели баллов подшкалы «Качество жизни» NIH-CPSI по данным исследований

Study	Treatment group			Control group			*MD*	95% CI	
	n	*M*	*SD*	*n*	*M*	*SD*		lower limit	upper limit
Dosta N.I. (2013) [15]	20	2.0	4.02	15	3.0	1.94	–1.0	–3.02	1.02
Tkachuk V.N. (2015) [28]	210	3.1	5.80	40	6.5	3.79	–3.4	–4.81	–1.99

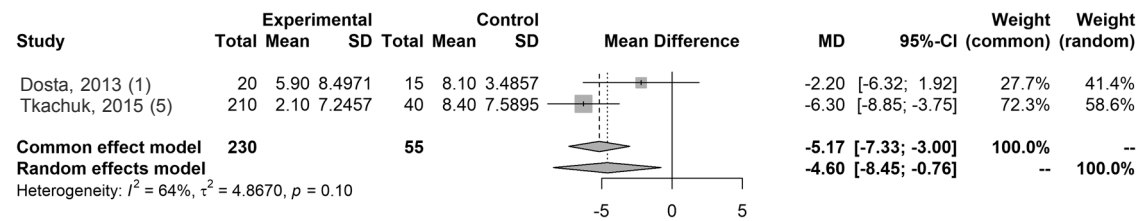

Fig. 8. Meta-analysis of changes in NIH-CPSI Pain subscale scores after treatment
Рис. 8. Метаанализ изменения баллов подшкалы «Боль» NIH-CPSI после лечения

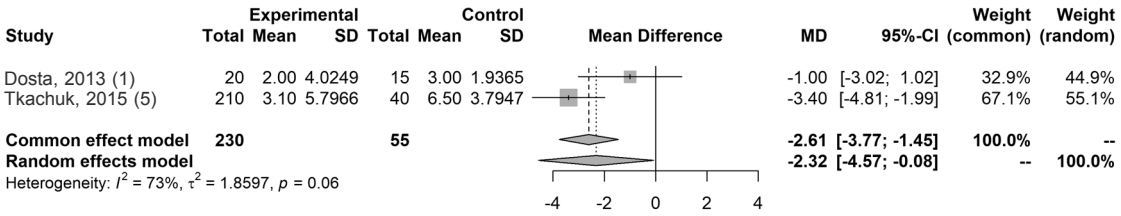

Fig. 9. Meta-analysis of change in NIH-CPSI Quality of Life subscale scores after treatment
Рис. 9. Метаанализ изменения баллов подшкалы «Качество жизни» NIH-CPSI после лечения

Table 10. Immunogram parameters according to the study by N.Yu. Noskov (2004) [27]
Таблица 10. Показатели иммунограммы у больных по данным исследования Н.Ю. Носкова (2004) [27]

Immunology parameters	Before treatment	After treatment			
		Treatment group		Control group	
		M ± *SD*	*p*	*M* ± *SD*	*p*
$CD3^+$ T cells, %	82.9 ± 9.4	69.4 ± 8.8	<0.01	79.5 ± 10.1	0.1
$CD4^+$ T cells, %	24.1 ± 3.8	41.6 ± 8.8	<0.01	35.4 ± 7.1	<0.05
$CD8^+$ T cells, %	18.1 ± 2.4	24.8 ± 3.5	<0.01	20.5 ± 1.7	<0.05
$CD22^+$ T cells, %	14.3 ± 0.9	23.6 ± 2.4	<0.01	19.4 ± 3.3	<0.05
PHA-induced lymphocyte activity, cpm	4310 ± 106	7231 ± 80	<0.01	4935 ± 215	<0.05
CH 100, RU	98.5 ± 5.3	169.8 ± 8.4	<0.01	109.1 ± 5.1	<0.05
Circulating immune complexes, RU	0.05 ± 0.008	0.07 ± 0.005	<0.05	0.06 ± 0.009	<0.05
CD4/CD8, RU	1.33 ± 0.3	1.68 ± 0.5	<0.01	1.73 ± 0.4	<0.01
IgM, g/L	0.5 ± 0.1	0.9 ± 0.3	<0.01	0.6 ± 0.3	<0.05
IgG, g/L	6.0 ± 0.4	10.3 ± 0.4	<0.01	8.3 ± 1.1	<0.05
IgA, g/L	2.2 ± 0.6	3.4 ± 0.7	<0.01	2.6 ± 0.5	<0.05

Note. M, mean; SD, standard deviation; MD, mean difference; CI, confidence interval; PHA, phytohemagglutinin.

patients had immunodeficiency with T-cell immunity disorders and decreased phagocytic activity. After treatment, the treatment group showed an increase in $CD3^+$ T-cells from 35.6 ± 2.9 to 49.3 ± 2.7% ($p < 0.01$), $CD4^+$ T-cells from 17.9 ± 2.1 to 32.4 ± 1.9% ($p < 0.01$), B-cells ($CD22^+$) from 14.3 ± 0.9 to 20.5 ± 1.8% ($p < 0.05$), T-helper/T-suppressor ratio from 1.1 ± 0.1 to 1.7 ± 0.3 ($p < 0.05$), and functional lymphocyte activity from 4,338 ± 209 to 7,396 ± 346 cpm ($p < 0.001$).

CONCLUSIONS

We found 9 non-randomized efficacy studies of combination therapy with Wobenzym in CBP patients vs. standard of care.

The meta-analysis revealed the following:

1. The majority of studies showed that therapy with Wobenzym in CBP patients significantly more often results in pathogen eradication compared to therapy without Wobenzym. The OR of the fixed effects model was 11.19 (95% CI 6.42, 19.50; $p = 0.00$); the OR of the random effects model was 11.22 (95.% CI 5.75, 21.88; $p = 0.00$).

2. Therapy with Wobenzym in CBP patients significantly decreases the QoL score compared to therapy without Wobenzym. The studies showed a significant between-group difference of 2 points. MD was –2.02 (95% CI –2.44, –1.59; $p = 0.00$) in the fixed effects model and –1.82 (95% CI –2.54, –1.11; $p = 0.00$) in the random effects model.

3. Therapy with Wobenzym in CBP patients significantly increases the linear blood flow velocity in prostate veins by more than 1 cm/s compared to therapy without Wobenzym. The studies showed a significant improvement in prostate blood flow. MD was 1.07 (95% CI 0.62, 1.51; $p = 0.00$) in the fixed effects model and 1.20 (95%

CI 0.42, 1.68; $p = 0.00$) in the random effects model. The result was significant, with a significant between-group difference.

4. Therapy with Wobenzym in CBP patients significantly increases the peak systolic velocity in prostate arteries compared to therapy without Wobenzym. The between-group difference was 3.5 cm/s. MD was 3.48 (95% CI 2.67, 4.29; $p = 0.00$) in the fixed effects model and 3.48 (95% CI 2.62, 4.34; $p = 0.00$) in the random effects model.

5. Therapy with Wobenzym in CBP patients significantly increases the maximum urine flow rate compared to therapy without Wobenzym. MD was 6.01 (95% CI 3.9, 8.11; $p = 0.00$) in the fixed effects model and 6.01 (95% CI 3.9, 8.11; $p = 0.00$) in the random effects model.

6. Therapy with Wobenzym in CBP patients significantly decreases the NIH-CPSI Pain domain score compared to therapy without Wobenzym. The between-group difference was 5 points. MD was –5.17 (95% CI –7.33, –3.0; $p = 0.00$) in the fixed effects model and –4.60 (95% CI –8.45, –0.76; $p = 0.02$) in the random effects model.

7. Therapy with Wobenzym in CBP patients significantly decreases the NIH-CPSI Quality of Life domain score compared to therapy without Wobenzym. The result was significant; however, heterogeneity was high. The between-group difference was 2 points. High heterogeneity can be explained by a small number of included studies. MD was –2.61 (95% CI –3.77, –1.45; $p = 0.00$) in the fixed effects model and –2.32 (95% CI –4.57, –0.08; $p = 0.04$) in the random effects model.

8. Therapy with Wobenzym in CBP patients provides a greater increase in $CD4^+$ T-cells, $CD8^+$ T-cells, lymphocyte activity, CH100, and IgM, IgG, and IgA.

Overall completeness and applicability of evidence

In general, all studies used the same Wobenzym dosage regimen and treatment duration. The age of study subjects varied widely, from young to older patients; thus, study findings can be applied to the population receiving Wobenzym in real-world practice.

Quality of evidence

None of the studies had a high risk of bias in any domain. The majority of risk domains had an unclear risk of bias.

Risk of bias during the review

We extracted the data without any limitations.

Agreement and disagreement with other studies and reviews

We could not find any other systematic reviews of the efficacy of Wobenzym in combination therapy for CBP in open sources.

Commercial impact

None of the studies had a conflict of interest to declare.

CONCLUSION

The systematic review and meta-analysis confirmed the positive effect of Wobenzym when added to combination therapy for CBP. Combination therapy including Wobenzym provides an 11-fold increase in pathogen eradication rate compared to therapy without Wobenzym. This is essential for the treatment of prostate infection and inflammation, and is linked to pathogenesis-oriented anti-inflammatory and antibiofilm effects of the drug, as well as its influence on pathogen mobility and adhesion. Moreover, combination therapy with Wobenzym enhances blood flow to the prostate, as indicated by improved arterial and venous microcirculation in the prostate tissues. This appears to be attributable to the drug's beneficial influence on the course of inflammation, as well as improvements in blood rheology and vascular platelet hemostasis.

When added to chronic prostatitis therapy, Wobenzym improves maximum urine flow rate and urination by reducing prostate tissue swelling. Therapy with Wobenzym decreases the severity of prostatitis symptoms, as indicated by a decrease in the NIH-CPSI score (Pain and Quality of Life domains) and the QoL score. These findings suggest reversal or reduction in symptoms and improvement in the quality of life of CBP patients in the study group.

When added to chronic prostatitis therapy, Wobenzym promotes immune defense, which is indicated by a greater increase in $CD4^+$ T-cells, $CD8^+$ T-cells, lymphocyte activity, CH100, and IgM, IgG, and IgA, compared to patients who did not receive Wobenzym.

Given the foregoing, the objective, significant positive effect of Wobenzym as part of combination therapy in CBP patients can be attributed to its pathogenetic action in this patient population.

To gather evidence and produce more reliable findings, randomized blinded studies with similar endpoints and follow-up periods should be conducted in CBP patients.

ADDITIONAL INFORMATION

Acknowledgements. The authors are grateful to a scientific agency Sciencefiles for assistance in the advanced statistical processing during the drafting of an article.

Authors' contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author:

Yu.A. Kupriyanov — data collection; A.V. Zaitsev — review of publications; A.N. Bernikov — data analysis; L.A. Khodyreva — writing the text of the manuscript; D.Yu. Pushkar — research concept, scientific editing, scientific guidance.

Funding source. This study was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

REFERENCES

1. Suvorov S, Tolstokorov S. Optimization of therapy of patients with chronic uretrogenic prostatitis. *Universum: Medicine and pharmacology*. 2019;(9):10–12. EDN: SXUBHX

2. Vermassen T, Van Praet C, Poelaert F, et al. Diagnostic accuracy of urinary prostate protein glycosylation profiling in prostatitis diagnosis. *Biochem Med (Zagreb)*. 2015;25(3):439–449. doi: 10.11613/BM.2015.045

3. Kwan ACF, Beahm NP. Fosfomycin for bacterial prostatitis: a review. *Int J Antimicrob Agents*. 2020;56(4):106106. doi: 10.1016/j.ijantimicag.2020.106106

4. Pushkar DYu, Rasner PI, Kotenko DV, et al. Specific features of lower urinary tract symptoms in men living in the Moscow Region. Results of the epidemiological study. *Urologiia*. 2018;(3):20–29. EDN: UVCSAJ doi: 10.18565/urology.2018.3.20-28

5. Suskind AM, Berry SH, Ewing BA, et al. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the RAND Interstitial cystitis epidemiology male study. *J Urol*. 2013;189(1):141–145. doi: 10.1016/j.juro.2012.08.088

6. Panchenko IA, Brusnev AB, Garmash ON, et al. Men's reproductive service based on the regional specialized center. *Experimental and clinical urology*. 2019;(2):20–25. EDN: QARIIS doi: 10.29188/2222-8543-2019-11-2-20-24

7. Shoskes DA, Nickel JC, Rackley RR, Pontari MA. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes. *Prostate Cancer Prostatic Dis*. 2009;12(2):177–183. doi: 10.1038/pcan.2008.42

8. Filimonov PN, Kulchavenya EV. Consequences of excessive fibrosis formation in patients with chronic prostatitis. *RMJ*. 2019;27(2):39–41. EDN: UDLZTH

9. Bouiller K, Zayet S, Lalloz PE, et al. Efficacy and safety of oral fosfomycin-trometamol in male urinary tract infections with multidrug-resistant enterobacterales. *Antibiotics (Basel)*. 2022;11(2):198. doi: 10.3390/antibiotics11020198

10. Shormanov IS, Solov'ev AS. Pathogenic mechanisms of pain in chronic bacterial prostatitis. *Experimental and clinical urology*. 2016;(3):96–101. EDN: YHTWRP

11. Smelov V, Perekalina T, Artemenko N, et al. Chlamydia trachomatis survival in the presence of two fluoroquinolones (lomefloxacin versus levofloxacin) in patients with chronic prostatitis syndrome. *Andrologia*. 2005;37(2–3):61–64. doi: 10.1111/j.1439-0272.2005.00654.x

12. uroweb.org [Internet]. EAU Guidelines. Edn. presented at the EAU Annual Congress Milan, Italy 2023. Available from: https://uroweb.org/guidelines/urological-infections

13. Wagenlehner FME, Naber KG. Prostatitis: the role of antibiotic treatment. *World J Urol*. 2003;21(2):105–108. doi: 10.1007/s00345-003-0333-4

14. Hu M, Wazir J, Ullah R, et al. Phytotherapy and physical therapy in the management of chronic prostatitis-chronic pelvic pain syndrome. *Int Urol Nephrol*. 2019;51(7):1081–1088. doi: 10.1007/s11255-019-02161-x

15. Dosta NI, Sevostianov NS. Efficiency of application enzymotherapy in complex treatment of a chronic bacterial prostatitis. *Medical News*. 2013;(12):72–76. EDN: RRSUBL

16. Sternin YI, Tetz BB, Knorring GYu. Modern possibilities of optimization of antibacterial therapy. *Glavnyi vrach uga Russia*. 2010;(3):17–20. EDN: XGIAJY (In Russ.)

17. Mikhailov IB, Sternin YuI. Selected issues of clinical pharmacology of systemic enzymotherapy. *Archive of Internal Medicine*. 2012;(1):15–19. EDN: RPEMEH doi: 10.20514/2226-6704-2012-0-1-15-19

18. Higgins J, Thomas J, editors. Cochrane handbook for systematic reviews of interventions. Available from: https://training.cochrane.org/handbook/current

19. Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions: Cochrane book series*. Chichester, England: Hoboken, New Jersey: Wiley-Blackwell, 2008. 649 p. doi: 10.1002/9780470712184

20. Rebrova OYu, Fedyaeva VK, Khachatryan GR. Adaptation and validation of the cochrane questionnarie to assess risks of bias in randomized controlled trials. *Medical technologies. Assessment and choice*. 2015;(1):9–17. EDN: RYRKUT

21. sites.google.com [Internet]. Risk of bias tools — robvis (visualization tool). Available from: https://sites.google.com/site/riskofbiastool/welcome/robvis-visualization-tool

22. gdt.gradepro.org [Internet]. GRADE handbook. Available from: https://gdt.gradepro.org/app/handbook/handbook.html

23. www.prisma-statement.org [Internet]. PRISMA flow diagram. Available from: http://www.prisma-statement.org/PRISMAStatement/FlowDiagram

24. Dzhalilov HN, Arbuliev KM, Dzhalilova DN, Gusniev NM. Improving medical and social rehabilitation of elderly patients and older with chronic bacterial prostatitis. *Ural Medical Journal*. 2020;(2):115–120. EDN: CRWPEB doi: 10.25694/URMJ.2020.02.28

25. Ershov EV. Evaluation of prostate blood circulation in patients with chronic prostatitis. *Nephrology (Saint-Petersburg)*. 2007;11(1):103–107. EDN: HZGOLV

26. Kodiri TR, Saydulloev L, Sayfulloev KU, et al. Efficacy of vobenzyme in the treatment of chronic prostatitis. *Scientific and Practical Journal of TIPPMC*. 2013;(2):160–161. EDN: RHMRQZ (In Russ.)

27. Noskov NYu. Use of vobenzyme in complex therapy of patients with chronic prostatitis. *Nephrology (Saint Petersburg)*. 2004;8(3):84–86. EDN: JUKPJL doi: 10.24884/1561-6274-2004-8-3-84-86

28. Tkachuk VN, Al-Shukri AS, Tkachuk IN, Sternin YI. The results of a 10-year efficacy study of proteolytic enzymes in patients with chronic prostatitis. *Urology reports (St. Petersburg)*. 2015;5(2):5–9. EDN: UKKJOV doi: 10.17816/uroved525-9

29. Tkachuk VN, Lukyanov AE, Noskov NY. Place of systemic enzymotherapy in complex treatment of patients with chronic prostatitis. *Physician's estate*. 2007;(5):36–41. (In Russ.)

30. Solihov DN. Vobenzyme in the treatment of chronic bacterial prostatitis. *DAN of the Republic of Tajikistan*. 2009;52(5):400–402. (In Russ.)

31. Dzhalilov KhN, Arbuliev KM, Saidov MS, et al. To the question of the use of drugs with a polymodal effect in the complex treatment of elderly and senile patients with recurrent chronic bacterial prostatitis. *Ural Medical Journal*. 2019;(15):154–160. EDN: PZVUCB doi: 10.25694/URMJ.2019.15.32

СПИСОК ЛИТЕРАТУРЫ

1. Суворов С.А., Толстокоров С.А. Оптимизация терапии больных хроническим уретрогенным простатитом // Universum: Медицина и фармакология. 2019. № 9. С. 10–12. EDN: SXUBHX
2. Vermassen T., Van Praet C., Poelaert F., et al. Diagnostic accuracy of urinary prostate protein glycosylation profiling in prostatitis diagnosis // Biochem Med (Zagreb). 2015. Vol. 25, N. 3. P. 439–449. doi: 10.11613/BM.2015.045
3. Kwan A.C.F., Beahm N.P. Fosfomycin for bacterial prostatitis: a review // Int J Antimicrob Agents. 2020. Vol. 56, N. 4. ID 106106. doi: 10.1016/j.ijantimicag.2020.106106
4. Пушкарь Д.Ю., Раснер П.И., Котенко Д.В., и др. Особенности симптомов нижних мочевыводящих путей у мужчин Московского региона. Результаты эпидемиологического исследования // Урология. 2018. № 3. С. 20–29. EDN: UVCSAJ doi: 10.18565/urology.2018.3.20-28
5. Suskind A.M., Berry S.H., Ewing B.A., et al. The prevalence and overlap of interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome in men: Results of the RAND Interstitial cystitis epidemiology male study // J Urol. 2013. Vol. 189, N. 1. P. 141–145. doi: 10.1016/j.juro.2012.08.088
6. Панченко И.А., Бруснев А.Б., Гармаш О.Н., и др. Служба репродуктивного мужского здоровья на примере краевого специализированного центра // Экспериментальная и клиническая урология. 2019. № 2. С. 20–25. EDN: QARIIS doi: 10.29188/2222-8543-2019-11-2-20-24
7. Shoskes D.A., Nickel J.C., Rackley R.R., Pontari M.A. Clinical phenotyping in chronic prostatitis/chronic pelvic pain syndrome and interstitial cystitis: a management strategy for urologic chronic pelvic pain syndromes // Prostate Cancer Prostatic Dis. 2009. Vol. 12, N. 2. P. 177–183. doi: 10.1038/pcan.2008.42
8. Филимонов П.Н., Кульчавеня Е.В. Последствия избыточного формирования фиброза у больных хроническим простатитом // РМЖ. 2019. Т. 27, № 2. С. 39–41. EDN: UDLZTH
9. Bouiller K., Zayet S., Lalloz P.E., et al. Efficacy and safety of oral fosfomycin-trometamol in male urinary tract infections with multidrug-resistant enterobacterales // Antibiotics (Basel). 2022. Vol. 11, N. 2. ID198. doi: 10.3390/antibiotics11020198
10. Шорманов И.С., Соловьев А.С. Патогенетические механизмы болевого синдрома при хроническом бактериальном простатите // Экспериментальная и клиническая урология. 2016. № 3. С. 96–101. EDN: YHTWRP
11. Smelov V., Perekalina T., Artemenko N., et al. Chlamydia trachomatis survival in the presence of two fluoroquinolones (lomefloxacin versus levofloxacin) in patients with chronic prostatitis syndrome // Andrologia. 2005. Vol. 37, N. 2–3. P. 61–64. doi: 10.1111/j.1439-0272.2005.00654.x
12. uroweb.org [Электронный ресурс]. EAU Guidelines. Edn. presented at the EAU Annual Congress Milan, Italy 2023. Режим доступа: https://uroweb.org/guidelines/urological-infections
13. Wagenlehner F.M.E., Naber K.G. Prostatitis: the role of antibiotic treatment // World J Urol. 2003. Vol. 21, N. 2. P. 105–108. doi: 10.1007/s00345-003-0333-4
14. Hu M., Wazir J., Ullah R., et al. Phytotherapy and physical therapy in the management of chronic prostatitis-chronic pelvic pain syndrome // Int Urol Nephrol. 2019. Vol. 51, N. 7. P. 1081–1088. doi: 10.1007/s11255-019-02161-x
15. Доста Н.И., Севостьянов Н.С. Эффективность применения энзимотерапии в комплексном лечении хронического бактериального простатита // Медицинские новости. 2013. № 12. С. 72–76. EDN: RRSUBL
16. Стернин Ю.И., Тец В.В., Кнорринг Г.Ю. Современные возможности оптимизации антибактериальной терапии // Главный врач Юга России. 2010. № 3. С. 17–20. EDN: XGIAJY
17. Михайлов И.Б., Стернин Ю.И. Избранные вопросы клинической фармакологии системной энзимотерапии // Архивъ внутренней медицины. 2012. № 1. С. 15–19. EDN: RPEMEH doi: 10.20514/2226-6704-2012-0-1-15-19
18. Higgins J., Thomas J., editors. Cochrane handbook for systematic reviews of interventions. Режим доступа: https://training.cochrane.org/handbook/current
19. Cochrane handbook for systematic reviews of interventions: Cochrane book series / edit by J.P.T. Higgins, S. Green. Chichester, England: Hoboken, New Jersey: Wiley-Blackwell, 2008. 649 p. doi: 10.1002/9780470712184
20. Реброва О.Ю., Федяева В.К., Хачатрян Г.Р. Адаптация и валидизация вопросника для оценки риска систематических ошибок в рандомизированных контролируемых испытаниях // Медицинские технологии. Оценка и выбор. 2015. № 1. С. 9–17. EDN: RYRKUT
21. sites.google.com [Электронный ресурс]. Risk of bias tools — robvis (visualization tool). Режим доступа: https://sites.google.com/site/riskofbiastool/welcome/robvis-visualization-tool
22. gdt.gradepro.org [Электронный ресурс]. GRADE handbook. Режим доступа: https://gdt.gradepro.org/app/handbook/handbook.html
23. www.prisma-statement.org [Электронный ресурс]. PRISMA flow diagram. Режим доступа: http://www.prisma-statement.org/PRISMAStatement/FlowDiagram
24. Джалилов Х.Н., Арбулиев К.М., Джалилова Д.Н., Гусниев Н.М. Совершенствование медико-социальной реабилитации пациентов пожилого возраста и старше с хроническим бактериальным простатитом // Уральский медицинский журнал. 2020. № 2. С. 115–120. EDN: CRWPEB doi: 10.25694/URMJ.2020.02.28
25. Ершов Е.В. Оценка кровообращения в предстательной железе у больных хроническим простатитом // Нефрология. 2007. Т. 11, № 1. С. 103–107. EDN: HZGOLV
26. Кодири Т.Р., Сайдуллоев Л., Сайфуллоев К.У., и др. Эффективность Вобэнзима при лечении хронического простатита // Научно-практический журнал ТИППМК. 2013. № 2. С. 160–161. EDN: RHMRQZ
27. Носков Н.Ю. Применение Вобэнзима в комплексной терапии больных хроническим простатитом // Нефрология. 2004. Т. 8, № 3. С. 84–86. EDN: JUKPJL doi: 10.24884/1561-6274-2004-8-3-84-86
28. Ткачук В.Н., Аль-Шукри А.С., Ткачук И.Н., Стернин Ю.И. Результаты 10-летнего исследования эффективности протеолитических энзимов у больных хроническим простатитом // Урологические ведомости. 2015. Т. 5, № 2. С. 5–9. EDN: UKKJOV doi: 10.17816/uroved525-9
29. Ткачук В.Н., Лукьянов А.Э., Носков Н.Ю. Место системной энзимотерапии в комплексном лечении больных хронически простатитом // Врачебное сословие. 2007. № 5. С. 36–41.
30. Солихов Д.Н. Вобэнзим в лечении хронического бактериального простатита // ДАН Республики Таджикистан. 2009. Т. 52, № 5. С. 400–402.
31. Джалилов Х.Н., Арбулиев К.М., Саидов М.С., и др. К вопросу об использовании препаратов с полимодальным действием в комплексной терапии пациентов пожилого и старческого возраста с рецидивирующим хроническим бактериальным простатитом // Уральский медицинский журнал. 2019. № 15. С. 154–160. EDN: PZVUCB doi: 10.25694/URMJ.2019.15.32

AUTHORS' INFO

Yuriy A. Kupriyanov, Cand. Sci. (Medicine), Associate Professor; ORCID: 0000-0002-5807-7591; eLibrary SPIN: 5203-9824; e-mail: dr.kupriyanov@mail.ru

Andrey V. Zaitsev, Dr. Sci. (Medicicne), Professor; ORCID: 0000-0001-2387-2361; eLibrary SPIN: 6223-5408; Scopus Author ID: 7201772210; e-mail: zaitcevandrew@mail.ru

Alexander N. Bernikov, Cand. Sci. (Medicine), Associate Professor; ORCID: 0000-0001-8361-585X; eLibrary SPIN: 9288-4518; e-mail: bernikov@mac.com

***Lyubov A. Khodyreva,** Dr. Sci. (Medicine); address: 9 Shariko-podshipnikovskaya st., Moscow, 115080, Russia; ORCID: 0000-0002-0751-4982; Scopus Author ID: 6602548630; eLibrary SPIN: 3565-5366; e-mail: khodyreva60@mail.ru

Dmitry Yu. Pushkar, Academician of the Russian Academy of Sciences, Dr. Sci. (Medicicne), Professor; ORCID: 0000-0002-6096-5723; Scopus Author ID: 24171496100; eLibrary SPIN: 8221-8306; e-mail: pushkardm@mail.ru

* Corresponding author / Автор, ответственный за переписку

ОБ АВТОРАХ

Юрий Александрович Куприянов, канд. мед. наук, доцент; ORCID: 0000-0002-5807-7591; eLibrary SPIN: 5203-9824; e-mail: dr.kupriyanov@mail.ru

Андрей Владимирович Зайцев, д-р мед. наук, профессор; ORCID: 0000-0001-2387-2361; eLibrary SPIN: 6223-5408; Scopus Author ID: 7201772210; e-mail: zaitcevandrew@mail.ru

Александр Николаевич Берников, канд. мед. наук, доцент; ORCID: 0000-0001-8361-585X; eLibrary SPIN: 9288-4518; e-mail: bernikov@mac.com

***Любовь Александровна Ходырева,** д-р мед. наук; адрес: Россия, 115080, Москва, Шарикоподшипниковская ул., д. 9; ORCID: 0000-0002-0751-4982; Scopus Author ID: 6602548630; eLibrary SPIN: 3565-5366; e-mail: khodyreva60@mail.ru

Дмитрий Юрьевич Пушкарь, академик РАН, д-р мед. наук, профессор; ORCID: 0000-0002-6096-5723; Scopus Author ID: 24171496100; eLibrary SPIN: 8221-8306; e-mail: pushkardm@mail.ru