Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ
(PHARMACY & PHARMACOLOGY)

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2025-13-6-487-499

Impact of CYP3A4*22 Genetic Variant and Plasma microRNA mir-27b Expression Level on Silodosin Steady-State Concentration and Therapy Outcomes in Patients with Benign Prostatic Hyperplasia: A Prospective Observational Trial

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Received 11 July 2025 | After peer review 15 Sep 2025 | Accepted 18 Oct 2025

Despite the proven efficacy of silodosin for lower urinary tract symptoms (LUTSs), significant interindividual variability in response to pharmacotherapy and the development of adverse events persists. Potential factors for this variability include pharmacogenetic and epigenetic mechanisms regulating drug metabolism.

The aim. To investigate the impact of CYP3A4*22 polymorphism and circulating microRNA miR-27b level on the pharmacokinetics, efficacy, and safety of silodosin in patients with benign prostatic hyperplasia (BPH).

Materials and methods. The study included 98 patients with LUTS due to BPH who were prescribed silodosin 8 mg/day for 8 weeks. IPSS and QoL dynamics, and the frequency of adverse events were assessed. The steady-state minimum concentration of silodosin (Css) was determined by HPLC-MS/MS. Genotyping for CYP3A4*22 was performed by real-time PCR. The expression level of plasma miR-27b was determined using RT-qPCR.

Results. Patients with the CT genotype (12.2%) had significantly higher Css values compared to carriers of the CC genotype (13.44 [6.35; 16.6] *vs* 6.15 [3.10; 11.31] ng/mL; $p = 0.005717$). Despite this, the reduction in symptom severity according to IPSS and improvement in QoL were comparable in both groups ($p > 0.05$). No correlation was found between Css and IPSS dynamics ($rs = -0.115554$, $p = 0.257195$). MiR-27b levels did not differ between genotypes and did not correlate with either Css or clinical outcomes. The structure of adverse events corresponded to the established safety profile of silodosin; no statistically significant differences were found between genotypic groups.

Conclusion. Carrying the CYP3A4*22 polymorphism is associated with increased silodosin exposure, but the clinical efficacy of therapy remains independent of this genetic marker. Data on the role of miR-27b in regulating pharmacokinetics and clinical outcomes in this population were not confirmed.

Keywords: silodosin; CYP3A4*22; pharmacogenetics; microRNA; miR-27b; benign prostatic hyperplasia

Abbreviations: BPH — benign prostatic hyperplasia; LUTSs — lower urinary tract symptoms; HPLC-MS/MS — high-performance liquid chromatography with tandem mass spectrometry; PCR — polymerase chain reaction; PVR — post-void residual volume; PV — prostate volume; US — ultrasound; AEs — adverse events; ICF — informed consent form; Css — minimum steady-state drug concentration in blood plasma; CYP3A4 — cytochrome P450 3A4; IPSS — International Prostate Symptom Score; QoL — Quality of Life Scale; Qmax — maximum urinary flow rate; RT-qPCR — Reverse Transcription Quantitative PCR; ADME — Absorption, Distribution, Metabolism, Excretion; P-gp (ABCB1) — P-glycoprotein.

For citation: Sh.P. Abdullaev, I.V. Bure, M.N. Shatokhin, Sh.P. Abdullaev, P.O. Bochkov, S.N. Tuchkova, K.B. Mirzaev, O.B. Loran, D.A. Sychev. Impact of CYP3A4*22 Genetic Variant and Plasma microRNA miR-27b Expression Level on Silodosin Steady-State Concentration and Therapy Outcomes in Patients with Benign Prostatic Hyperplasia: A Prospective Observational Trial. *Pharmacy & Pharmacology.* 2025;13(6):487-499. **DOI:** 10.19163/2307-9266-2025-13-6-487-499

Для цитирования: Ш.П. Абдуллаев, И.В. Буре, М.Н. Шатохин, Ш.П. Абдуллаев, П.О. Бочков, С.Н. Тучкова, К.Б. Мирзаев, О.Б. Лоран, Д.А. Сычев. Влияние генетического варианта CYP3A4*22 и уровня экспрессии плазменной микроРНК miR-27b на равновесную концентрацию силодозина и результаты терапии у пациентов с доброкачественной гиперплазией предстательной железы: проспективное обсервационное исследование. *Фармация и фармакология.* 2025;13(6):487-499. **DOI:** 10.19163/2307-9266-2025-13-6-487-499

RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY
(ФАРМАЦИЯ И ФАРМАКОЛОГИЯ)

Влияние генетического варианта CYP3A4*22 и уровня экспрессии плазменной микроРНК miR-27b на равновесную концентрацию силодозина и результаты терапии у пациентов с доброкачественной гиперплазией предстательной железы: проспективное обсервационное исследование

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Получена 11.07.2025 После рецензирования 15.09.2025 Принята к печати 18.10.2025

Несмотря на доказанную эффективность силодозина при симптомах нижних мочевых путей (СНМП), сохраняется значительная межиндивидуальная вариабельность ответа на фармакотерапию и развитие нежелательных явлений. Потенциальными факторами такой вариабельности являются фармакогенетические и эпигенетические механизмы регуляции метаболизма препарата.

Цель. Оценить влияние полиморфизма CYP3A4*22 и уровня циркулирующей микроРНК miR-27b на фармакокинетику, эффективность и безопасность силодозина у пациентов с доброкачественной гиперплазией предстательной железы (ДГПЖ).

Материалы и методы. В исследование включено 98 пациентов с СНМП при ДГПЖ, которым назначался силодозин 8 мг/сут в течение 8 недель. Оценивались динамика IPSS и QoL, частота нежелательных явлений. Равновесная минимальная концентрация силодозина (Css) определялась методом ВЭЖХ-МС/МС. Генотипирование по CYP3A4*22 проводили методом ПЦР в реальном времени. Уровень экспрессии плазменной miR-27b определяли с помощью RT-qPCR.

Результаты. Пациенты с генотипом CT (12,2%) имели достоверно более высокие значения Css по сравнению с носителями генотипа CC (13,44 [6,35; 16,6] против 6,15 [3,10; 11,31] нг/мл; p=0,005717). Несмотря на это, снижение выраженности симптомов по IPSS и улучшение QoL были сопоставимыми в обеих группах (p >0,05). Корреляции между Css и динамикой IPSS выявлено не было (rs=-0,115554, p=0,257195). Уровни miR-27b не различались между генотипами и не коррелировали ни с Css, ни с клиническими исходами. Структура нежелательных явлений соответствовала установленному профилю безопасности силодозина; статистически значимых различий между генотипическими группами не установлено.

Заключение. Носительство полиморфизма CYP3A4*22 ассоциируется с повышенной экспозицией силодозина, однако клиническая эффективность терапии остаётся независимой от указанного генетического маркёра. Данные о роли miR-27b в регуляции фармакокинетики и клинических исходов в данной популяции не подтвердились.

Ключевые слова: силодозин; CYP3A4*22; фармакогенетика; микроРНК; miR-27b; доброкачественная гиперплазия предстательной железы

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DOI: 10.19163/2307-9266-2025-13-6-487-499

Список сокращений: ДГПЖ — доброкачественная гиперплазия предстательной железы; СНМП — симптомы нижних мочевых путей; ВЭЖХ-МС/МС — высокоэффективная жидкостная хроматография с тандемной масс-спектрометрией; ПЦР — полимеразная цепная реакция; ООМ — объём остаточной мочи; ОП — объём простаты; УЗИ — ультразвуковое исследование; НЯ — нежелательные явления; ИДС — информированное добровольное согласие; Css min — минимальная равновесная концентрация препарата в плазме крови; CYP3A4 — цитохром P450 3A4; IPSS — Международная шкала оценки простатических симптомов; QoL — шкала оценки качества жизни; Qmax — максимальная скорость потока мочи; RT-qPCR — полимеразная цепная реакция в реальном времени с обратной транскрипцией; ADME — всасывание, распределение, метаболизм и выведение; P-gp (ABCB1) — P-гликопротеин.

INTRODUCTION

Benign prostatic hyperplasia (BPH) refers to the benign growth or hyperplasia of prostate tissue and is histologically defined by an increase in glandular epithelial tissue, smooth muscle, and connective tissue in the transition zone of the prostate [1, 2]. A meta-analysis including data from 25 countries showed that the lifetime prevalence of BPH is 26.2% (95% confidence interval [CI]: 22.8–29.6%) [3]. Forecasts indicate a global increase in the incidence and prevalence of BPH from approximately 962 and 7879 cases per 100,000 people in 2022 to approximately 999 and 8621 cases by 2035 [4]. According to data from the US Medicare program for 2019, annual global healthcare costs associated with BPH are estimated at approximately US$73.8 billion per year, based on US spending trends [5].

Modern pharmacotherapy for BPH includes several classes of drugs: 5α-reductase inhibitors, which affect prostate volume, and α1-blockers, which rapidly improve urodynamics by relaxing the smooth muscles of the prostate, bladder neck, and prostatic urethra. Among α1-blockers, silodosin occupies a special place as a highly selective α1A-adrenoceptor antagonist, providing a marked reduction in obstructive and irritative symptoms with minimal effect on systemic blood pressure. Although α1-blockers are included in clinical guidelines for the treatment of patients with lower urinary tract symptoms (LUTS), the number of patients with therapy-resistant disease and patients with adverse side effects remains high [6, 7].

CYP3A group isozymes, characterized by exceptionally broad substrate specificity, catalyze the metabolism of more than half of the drugs used in clinical practice.

Among them, *CYP3A4* is the main hepatic isoform, characterized by high expression and broad substrate specificity [8, 9]. This enzyme catalyzes the oxidation of a large number of drugs, including those used in urological practice for the treatment of LUTS. The *CYP3A4* gene exhibits marked polymorphism, and some of its variants, such as CYP3A4*22 (rs35599367), are associated with reduced enzyme expression and activity, which can lead to slowed drug metabolism and an increased risk of dose-dependent adverse reactions [10, 11]. Thus, changes in the efficacy and safety profiles of silodosin may also depend on variations in the *CYP3A4* gene, which determines the pharmacodynamic (PD) and pharmacokinetic (PK) parameters of the drug.

CYP3A4 catalyzes the oxidation of silodosin. Drugs that are inhibitors of *CYP3A4* activity (e.g., ketoconazole) can affect the PK and PD of silodosin, increasing its plasma concentration[1].

Considering the key role of cytochrome P450 isozymes in the metabolism of α1-blockers, one cannot ignore modern concepts of the multilevel regulation of their activity. In addition to well-studied genetic polymorphisms, researchers are paying increasing attention to epigenetic regulation, in particular, the involvement of microRNAs in the control of the expression of cytochrome P450 system enzymes. Previous studies have assessed the correlation between miR-27b levels and *CYP3A* activity, measured by *N*-demethylation of dextromethorphan and 6β-hydroxylation of testosterone, as well as the expression of CYP3A4, *VDR*, and *PPAR*-α genes in 20 human liver samples. A significant relationship was found between circulating miR-27b levels and the 4β-hydroxycholesterol ratio (p = 0.04), as well as between liver miR-27b levels and CYP3A activity, measured by N-demethylation of dextromethorphan (p = 0.04) [12]. Individual differences in *CYP3A4* activity, due to genetic or epigenetic factors, may play a significant role in interindividual variability in the

[1] U.S. Food and Drug Administration. Rapaflo (Silodosin) label; 2013. Available from: https://www.accessdata. fda.gov/drugsatfda_docs/label/2013/022206s012lbl.pdf

pharmacokinetics, efficacy, and safety of therapy with silodosin.

THE AIM. To study the effect of the CYP3A4*22 (rs35599367, 15389 C>T) genetic polymorphism on the concentration, as well as on the efficacy and safety of silodosin. Data on the expression level of plasma miR-27b, hypothetically characterizing the expression of the *CYP3A4* metabolizing enzyme, were used.

MATERIALS AND METHODS

Study design

A prospective observational trial was conducted from December 11, 2023 to May 30, 2025. The study involved patients receiving outpatient treatment at the Department of Endoscopic Urology of the Russian Medical Academy of Continuous Professional Education. Before inclusion in the study, each patient signed an informed voluntary consent form (ICF).

The study involved 98 male patients with complaints of LUTS and a diagnosis of BPH. Patients were prescribed silodosin at a dose of 8 mg/day according to indications. Silodosin therapy was started from the time of the patient's visit, and observation continued for at least 8 weeks. Treatment was prescribed in accordance with the National Clinical Guidelines for the treatment of patients with BPH[2].

Eligibility criteria

Inclusion criteria: male gender; age over 18 years; signed ICF form; diagnosis of benign prostatic hyperplasia" (N40 according to ICD-10); complaints of moderately or severely expressed LUTS, assessed by the IPSS scale >7 points.

Exclusion criteria: complicated BPH; any other causes other than BPH that may, in the opinion of the researchers, lead to dysuria or changes in urinary flow rate (e.g., neurogenic bladder, bladder neck stricture, urethral stricture, acute or chronic prostatitis, acute or chronic urinary tract infections); concomitant oncological diseases; concomitant severe cardiovascular (e.g., unstable angina, recent myocardial infarction, or poorly controlled arterial hypertension) and cerebrovascular (recent stroke or spinal cord injuries) diseases; renal and hepatic insufficiency.

[2] Clinical Guidelines. Benign prostatic hyperplasia. Ministry of Health of the Russian Federation; 2024. Available from: https://cr.minzdrav.gov.ru/preview-cr/6_2. Russian

Assessment of the efficacy and safety of therapy

The efficacy of silodosin therapy was assessed using a complex of clinical (assessment of LUTS manifestation using the IPSS questionnaire) and instrumental (determination of maximum urinary flow rate (Qmax), determination of residual urine (PVR), and prostate volume (PV) according to US data) methods. IPSS assessment was performed on days 1, 14, 28, and 56 of treatment and observation. Instrumental assessment of the efficacy of therapy was performed on days 1 and 56 of silodosin treatment. The safety of therapy was assessed by recording the development of adverse events (AEs) during the entire period of patient observation.

Genotyping

On the day of inclusion in the study, each patient had 4 mL of blood drawn into disposable sterile vacuum tubes with EDTA for subsequent genotyping. The collection of biomaterial, which was carried out simultaneously with routine tests, did not require additional venipunctures. The biomaterial was frozen at -20°C, transported to the laboratory, and subsequently stored at -70°C.

Genotyping for the CYP3A4*22 (15389 C>T, rs35599367) allelic variant was performed using TaqMan® SNP Genotyping Assays and TaqMan Universal Master Mix II, without UNG (Applied Biosystems, Foster City, USA) reagent kits according to the manufacturer's instructions.

The carriage of polymorphic markers was determined by real-time polymerase chain reaction (PCR) on a Real-Time CFX96 Touch instrument (Bio-Rad Laboratories, Inc., USA).

Determination of silodosin plasma concentration

To determine the minimum steady-state residual concentration values of silodosin in blood plasma (Css), venous blood samples were collected 5 days after the start of silodosin administration. The concentration of the drug in plasma was determined by a combined HPLC-MS/MS method on an Agilent 1200 Liquid Chromatograph (Agilent Technologies Inc., USA, 2008) using a triple quadrupole mass spectrometric detector AgilentTripleQuad LC/MS 6410. An Agilent Polaris 3 C18-A column (50 mm × 3.0 mm, 3.0 µm) was used. Separation was performed at a column temperature of

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DOI: 10.19163/2307-9266-2025-13-6-487-499

40°C in gradient elution mode by mixing mobile phase components: solution "A" (1 ml of concentrated formic acid was diluted with deionized water to a total volume of 1 L) and solution "B" (1 mL of concentrated formic acid was diluted with acetonitrile to a total volume of 1 L).

Sample preparation was performed by plasma protein precipitation. Plasma samples were thawed at room temperature. Then, 100 µL of plasma was transferred to Eppendorf plastic tubes, 250 µL of a mixture of methanol with 0.1% hydrochloric acid (in a ratio of 9:1) was added, mixed on a Vortex shaker (Elmi Ltd., Latvia) and left for 10 min. Then the samples were mixed again. The resulting samples were then centrifuged (CM-6MT, ELMI, Latvia) at 10,000 rpm for 10 min. The supernatant was transferred to chromatographic vials and placed on a chromatograph autosampler for subsequent analysis.

Silodosin spectra were recorded on an AgilentTripleQuad LC/MS 6410 mass spectrometric detector with positive electrospray ionization in multiple molecular reaction mode. Nebulizer gas pressure was 35 psi. The drying gas flow rate was 10 L/min, the ion source temperature was 350°C. The fragmentation voltage was 135 V, the collision cell voltage was 30 V. Under these conditions, the limit of quantification of silodosin was 1 ng/mL.

Data processing was performed using Agilent MassHunter Workstation Software LC/MS Data Acquisition for 6400 Series Triple Quadrupole (Version B.08.02).

Determination of plasma microRNA levels

Isolation of total RNA from blood plasma

To determine plasma microRNA levels, venous blood samples were collected in sterile tubes containing EDTA on day 5 of therapy. The closed blood tube was inverted several times to mix the blood with the anticoagulant. To obtain plasma, the tube was centrifuged (CM-6MT, ELMI, Latvia) for 10 min at 2000 g, after which the supernatant was transferred to sterile tubes with a volume of 2 or 1.5 mL and stored at -80°C until further use.

Then, 300 µL of plasma was lysed in 1 mL of Qiazol reagent, followed by the addition of 250 µL of chloroform. The solution was mixed thoroughly for 30 s, then incubated for 2–3 min at room temperature. After centrifugation at 12000 g for 15 min at 4°C, the upper aqueous phase was carefully removed and transferred to a tube with 0.5 mL of 100% isopropanol. The solution was mixed thoroughly by inverting the tube and frozen at -20°C for at least 1 h. After that, the tube was centrifuged at 12000 g for 10 min at 4°C. The precipitate remaining at the bottom of the tube after removal of the supernatant was washed with 1 ml of 75% ethanol, followed by centrifugation at 12000 g for 5 min at 4°C. The resulting precipitate was dissolved in 20 µL of RNase-free water, preheated to 60°C, and incubated for 5–10 min at 60°C. The concentration and purity of the obtained RNA were evaluated on a NanoDrop 2000 microvolume spectrophotometer (Thermo Fisher Scientific, New York, USA). The isolation process was repeated for each sample until sufficient RNA was obtained for the next steps. After mixing and precipitation, the samples were frozen at -20°C for short-term storage and at -80°C for long-term storage.

Quantitative assessment of microRNA expression levels by real-time PCR

Reverse transcription was performed using miRCURY LNA RT kit (Qiagen, Germany) and miRCURY LNA RNA Spike-in kit (Qiagen, Germany) according to the recommended protocol with modifications. To obtain DNA, 150 ng of total RNA isolated from each sample was used, which was added to the reaction mixture (4 µL 5× miRCURY RT Reaction Buffer, 1 µl 10x miRCURY RT Enzyme Mix, 2 µL of matrix for exogenous control cel-miR-39-3p and RNase-free water to 20 µl) and incubated for 60 min at 42°C, followed by increasing the temperature to 95°C for 5 min to inactivate the transcriptase. Real-time PCR was performed in 3 replicates for each analyzed microRNA, as well as exogenous control cel-miR-39-3p, using miRCURY LNA SYBR Green PCR kit (Qiagen), presynthesized primer miRCURY LNA miRNA Probe PCR Assay (Qiagen) for control and primers selected in the laboratory for the analyzed microRNAs (sequences are listed in Table 1) in a reaction mixture volume of 13 µl (3 µl of the obtained cDNA, 5 µL 2x miRCURY SYBR Green Master Mix, 1 µL 10x miRCURY LNA miRNA Probe PCR Assay to the studied microRNAs and RNase-free water to 13 µL). Real-time PCR was performed on a CFX96 Real-Time PCR Detection System (Bio-

Rad, Hercules, USA) according to the manufacturer's recommended program (2 min at 95°C and 40 two-step cycles [95°C — 10 s, 56°C — 60 s]). MicroRNA expression was normalized to the exogenous control cel-miR-39-3p and calculated using the 2-ΔΔCt method. For miR-27b-3p, the following primer sequence was used — 5'-TTCACAGTGGCTAAGTTCTGCA-3'.

Ethics approval

The study was approved by the meeting of the Local Ethics Committee of the Russian Medical Academy of Continuous Professional Education (Protocol No. 16 dated December 04, 2023).

Statistical analysis

Statistical analysis was performed using Statsoft Statistica 12.0 (Dell Statistica, Tulsa, OK, USA). Results of the study were performed using non-parametric statistics due to the absence of normal data distribution, which was checked using the Shapiro-Wilk W-test.

The Mann-Whitney *U*-test was used to compare two samples of continuous independent data, and the Wilcoxon test was used to compare two dependent samples. In the case of multiple comparisons, we calculated adjusted *p*-values using the Benjamini-Hochberg procedure. The study data are presented as median and interquartile range (Me [Q1; Q3]).

Pearson's Chi2 test was used to analyze the distribution of alleles in the sample (assessment of Hardy-Weinberg equilibrium). Correlation analysis was performed using the non-parametric Spearman test, taking into account the non-normal of the sample distribution.

The significance of the identified differences and correlations in all types of analysis was considered at the level of $p < 0.05$.

RESULTS

Baseline characteristics of patients

The study included 98 male patients with BPH and LUTS (median age — 70 [64.74; 75.50], BMI — 26.79 [25.18; 29.38] kg/m^2). Most patients had cardiovascular pathology: hypertension — 60 (61.2%), coronary heart disease — 20 (20.4%), type 2 diabetes mellitus — 3 (3.1%) and urological diseases (23.8%). More detailed clinical and demographic data are presented in Table 1.

Patients were pro-genotyped for the CYP3A4*22 allelic variant (c.522-191C>T, rs35599367): the number of patients with the CC genotype was 86 (87.75 %); with the CT genotype — 12 (12.25%); with the TT genotype — not established.

The distribution of genotypes corresponded to the Hardy-Weinberg equilibrium (χ^2=0.417, p = 0.812).

Main study results

The results of the analysis of data obtained in assessing the effectiveness of LUTS therapy in BPH according to IPSS and assessing the quality of life according to the QoL scale at 1, 2, 4 and 8 weeks of follow-up in patients receiving silodosin are presented in Table 2.

The dynamics of changes in IPSS scores in patients with different genotypes is shown in Figure 1. At visit 1, statistically significant differences were revealed in the groups of patients with different genotypes: for patients with the CC genotype, IPSS was higher 18 [14.0; 25.0] *vs* 11.0 [9.0; 15.0] for the CT group (p = 0.000112). By the second and fourth week, statistically significant differences between the groups persisted — $p < 0.0001$. At the last 8th week of the study, statistically significant differences also persisted: genotype CC — 13.5 [10.0; 17.0], CT —5.0 [3.0; 7.0] (p = 0.000035). The QoL quality of life assessment scale showed the same dynamics of changes in scores as the IPSS scale (Figs. 1A and 1B).

It is worth noting that the overall dynamics of changes in IPSS (d IPSS1-4) and QoL (d QoL1-4) between the groups throughout the 8-week observation period did not differ: for CC — -6.0 [-8.0; -5.0] *vs* -7.0 [-9.5; -2.5] for CT (p = 0.952101) for IPSS; for CC — -2.0 [-3.0; -1.0] *vs* -2.0 [-2.5; -1.0] for CT (p = 0.425932; Figs. 1C and 1D).

Table 3 summarizes the data on the results of determining Css silodosin. A statistically significant difference was found in patients with different genotypes: Css was higher in patients with CT — 13.44 [6.35; 16.6] *vs* 6.15 [3.10; 11.31] ng/mL with CC (p = 0.005717; Fig. 2A). Spearman correlation analysis did not reveal a statistically significant correlation between the Css silodosin index and the magnitude of the overall change in IPSS between the first and last visit (d IPSS1-4) — rs = -0.115554, p = 0.257195 (Fig. 2B, Table 3).

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Table 1 — Clinical and demographic characteristics of patients

Indicators	Total patient cohort (*n*=98)
Age, Me [Q1; Q3], years	70 [64,74; 75,50]
BMI, Me [Q1; Q3], kg/m^2	26,79 [25,18; 29,38]
Smoking, *n*	23
Alcohol, *n*	16
Laboratory parameters at the time of inclusion in the study	
Creatinine, Me [Q1; Q3], mmol/L	91.0 [81.5; 102.0]
Urea, Me [Q1; Q3], mmol/L	5.5 [4.6; 6.5]
Relative density, Me [Q1; Q3], g/L	1019.5 [1015.0; 1025.75]
pH, Me [Q1; Q3],	6.0 [5.5; 6.0]
Hemoglobin, Me [Q1; Q3], g/L	148.5 [145.0; 158.0]
Erythrocytes, Me [Q1; Q3], 10^9/L	4.83 [4.71; 5.01]
Leukocytes, Me [Q1; Q3], 10^9/L	6.30 [5.77; 7.25]
Platelets, Me [Q1; Q3], 10^9/L	235.0 [190.0; 269.75]
Erythrocyte sedimentation rate, Me [Q1; Q3], mm/hour	6.0 [4.0; 7.75]
Prostate-specific antigen, Me [Q1; Q3], ng/mL	1.94 [0.89; 3.34]
Concomitant diseases, *n* (%)	
Cardiovascular:	
hypertension	60 (61.2%)
ischemic heart disease	20 (20.4%)
dyslipidemia	18 (18.4%)
others	3 (3.1%)
Endocrine:	
type 2 diabetes mellitus	3 (3.1%)
Gastroenterological:	
pancreatitis	3 (3.1%)
Urological:	
urolithiasis	3 (3.1%)

Table 2 — Results of patient assessment on the IPSS and QoL scales at 1, 2, 4, and 8 weeks of follow-up

Indicator	Total cohort (*n*=98)	CC (*n*=86)	CT (*n*=12)	*p*-value
Visit 1 (at the time of inclusion)				
IPSS	11.5 [10.0; 15.0]	18 [14.0; 25.0]	11.0 [9.0; 15.0]	0.000112*
QoL	4 [4.0; 4.0]	4 [4.0; 4.0]	5.0 [4.0; 6.0]	0.003899*
Visit 2 (2 weeks)				
IPSS	9.0 [6.0; 11.0]	13.0 [10.5; 17.5]	8.5 [6.0; 10.0]	0.000215*
QoL	3.0 [3.0; 4.0]	3.0 [3.0; 3.0]	4.5 [3.0; 5.5]	0.001576*
Visit 3 (4 weeks)				
IPSS	7.0 [4.0; 13.0]	15.0 [10.5; 17.5]	6.0 [4.0; 10.0]	0.000046*
QoL	2.0 [2.0; 3.0]	2.0 [2.0; 3.0]	4.0 [2.5; 4.5]	0.002806*
Visit 4 (8 weeks)				
IPSS	6.0 [3.0; 12.00]	13.5 [10.0; 17.0]	5.0 [3.0; 7.0]	0.000035*
QoL	2.0 [1.0; 3.0]	2.0 [1.0; 3.0]	2.5 [2.0; 4.5]	0.016612*
Difference between Visits 1 and 4				
d $IPSS_{1-4}$	-6.0 [-9.0; -5.0]	-6.0 [-8.0; -5.0]	-7.0 [-9.5; -2.5]	0.952101
d QoL_{1-4}	-2 [-3.0; -1;0]	-2.0 [-3.0; -1.0]	-2.0 [-2.5; -1.0]	0.425932

Note: d IPSS1-4 — change in IPSS scores from baseline to day 56 of observation; d QoL1-4 — change in QoL quality of life scale scores from baseline to day 56 of observation; * — differences are statistically significant.

Table 3 — Steady-state concentration values of silodosin and assessment of plasma miR-27b expression levels in patients with different genotypes for the CYP3A4*22 polymorphic marker

Parameter	Total cohort (*n*=98)	CC (*n*=86)	CT (*n*=12)	*p*-value
Css, ng/mL	7.30 [3.20; 11.50]	6.15 [3.10; 11.31]	13.44 [6.35; 16.6]	0.005717*
ΔΔCt miR-27b	0.44 [0.12; 1.23]	0.47 [0.13; 1.23]	0.35 [0.087; 1.29]	0.815755

Note: * — differences are statistically significant.

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
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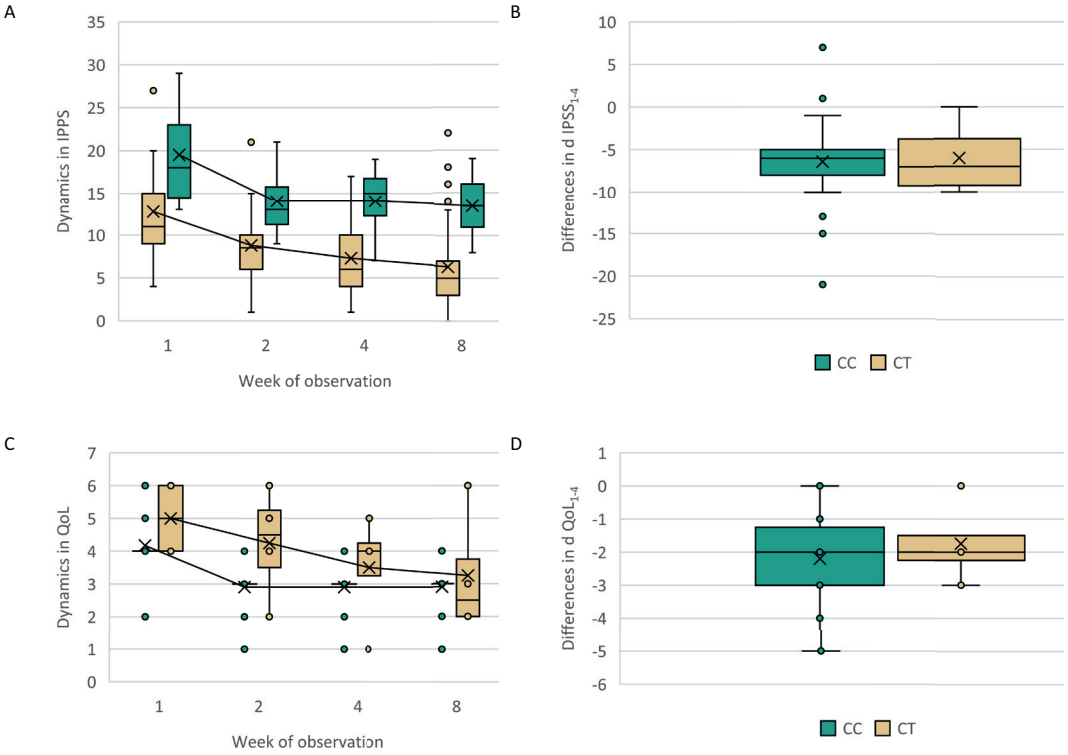

Figure 1 — Dynamics of changes in IPSS scores and QoL quality of life assessment in patients with different genotypes for the CYP3A4*22 polymorphic marker (rs35599367)

Note: A, B — data are presented as median and interquartile range — lines connect medians in different weeks of observation; C, D — differences in IPSS and QoL scores between the first and last day of observation.

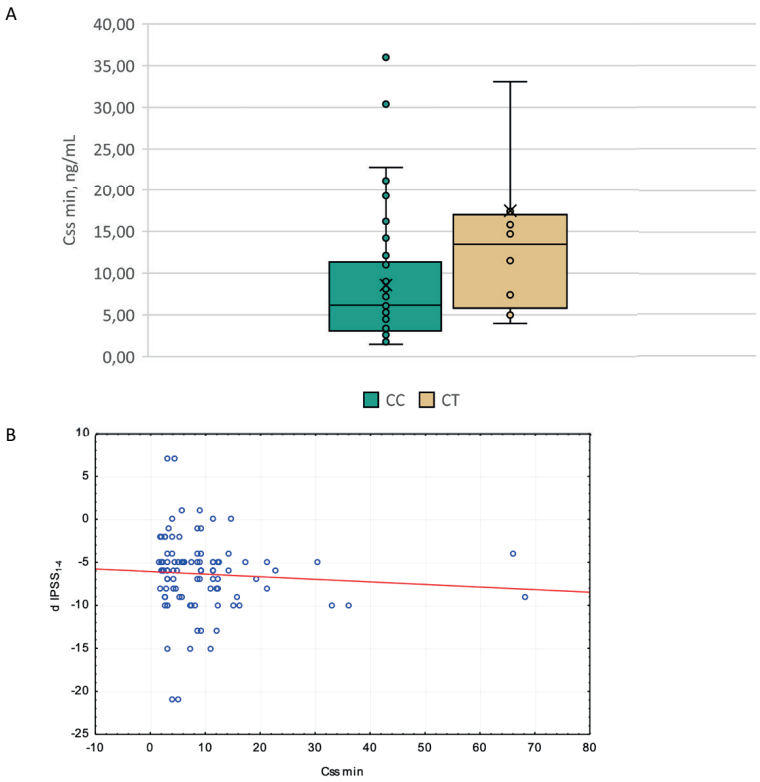

Figure 2 — Differences in Css silodosin values in patients with different genotypes for the CYP3A4*22 polymorphic marker.

Note: A — data are presented as median and interquartile range; B — relationship between Css silodosin value and d IPSS1-4 value in patients with lower urinary tract symptoms

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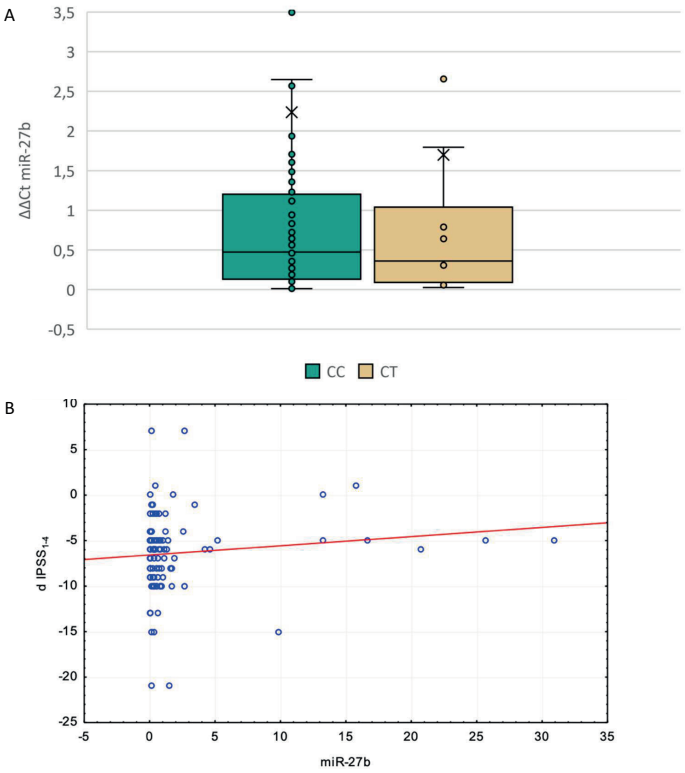

Figure 3 — Differences in Css silodosin values in patients with different genotypes for the CYP3A4*22 polymorphic marker.

Note: A — data are presented as median and interquartile range; B — relationship between ΔΔCt miR-27b value and d IPSS1-4 value in patients with lower urinary tract symptoms.

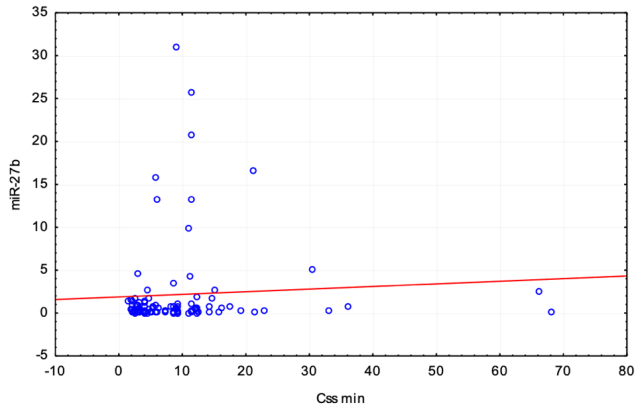

Figure 4 — Relationship between Css silodosin value and ΔΔCt miR-27b value in patients with lower urinary tract symptoms.

Table 4 – Frequency of adverse events in the study group, *n* (%)

Adverse events	Total cohort (*n*=98)	CC (*n*=86)	CT (*n*=12)
Retrograde ejaculation	6 (14.63)	6 (17.14)	0
Orthostatic hypotension	8 (19.51)	5 (14.29)	3 (50)
Hypertension	3 (7.32)	3 (8.57)	0
Dizziness	6 (14.63)	6 (17.14)	0
Headaches	3 (7.32)	0 (0)	3 (50)
Rhinitis	12 (29.27)	12 (34.29)	0
Back pain	3 (7.32)	3 (8.57)	0
Total	41 (100)	35 (100)	6 (100)

Analysis of the results of the pharmacotranscriptomics did not reveal a statistically significant difference in miR-27b levels in blood plasma in patients with different genotypes (Fig. 3A): CC — 0.47 [0.13; 1.23] *vs* CT — 0.35 [0.087; 1.29] (p = 0.815755). Correlation analysis revealed no associations between miR-27b concentration and the magnitude of the total change in d IPSS1-4 — rs = 0.055974, p = 0.584080 (Fig. 3B, Table 3).

The study found no correlation between microRNA concentration and the equilibrium concentration of silodosin — rs = 0.119251, p = 0.242178.

Safety assessment

During the study, 41 cases of adverse events (AEs) were noted in patients (Table 4). The most common were rhinitis — 12 (29.27%), orthostatic hypotension — 8 (19.51%), retrograde ejaculation — 6 (14.63%), and dizziness — 6 (14.63%). Less commonly, headaches were noted — 3 (7.32%), back pain — 3 (7.32%), and hypertension — 3 (7.32%). Due to the small number of events in the subgroups, no statistically significant differences were obtained, and the calculation of relative risks was not performed.

DISCUSSION

The results of the study revealed a statistically significant difference between the equilibrium concentration values of silodosin in patients with different CYP3A4*22 genotypes — in patients with the C allele, the equilibrium concentration of the drug was lower than in patients with the T allele (p = 0.005717). Apparently, this is due to the reduced rate of biotransformation and elimination of silodosin in patients with the T allele, which, in turn, leads to the accumulation of the drug in the blood plasma. This may lead to an increased risk of adverse reactions.

Statistical analysis of data on the clinical efficacy profile of silodosin in patients with different CYP3A4*22 genotypes revealed that already at visit 1, patients with the CC genotype had more pronounced symptoms compared to CT carriers (IPSS: 18 *vs* 11 points; $p < 0.001$). This difference persisted at 2, 4, and 8 weeks of follow-up. At the same time, the decrease in symptoms in both groups was comparable (delta IPSS: -6.0 *vs* -7.0 points; p = 0.952101), which indicates the same relative effectiveness of therapy regardless of genotype. This result may indicate that the clinical effect of silodosin is found out in a wide therapeutic range of concentrations and does not directly depend on carrying the CYP3A4*22 polymorphism.

Analyzing the relationship between the efficacy profile (dynamics of changes in dIPSS1-4 indicators) and the equilibrium minimum concentration of silodosin (Css), we did not reveal a statistically significant correlation (rs = -0.115554, p = 0.257195). This indicates that the clinical efficacy of the drug does not directly depend on its plasma levels. At the same time, the result is consistent with the data obtained for other α1-adrenoblockers, such as, for example, tamsulosin and doxazosin, for which it was also shown that the severity of the clinical response is determined by the characteristics of interaction with α1A-adrenoreceptors, the characteristics of distribution/binding in the prostate tissue, and the individual sensitivity of the patient's receptor apparatus [13–15]. This lack of a direct "concentration-effect" relationship can be explained by the onset of a therapeutic "plateau" — when the therapeutic effect of the drug is achieved even with a relatively low exposure in some patients, and a further increase in exposure is not accompanied by an increase in the symptomatic effect, but may increase the risk of adverse events [7, 13]. In addition, in the pathogenesis of lower urinary tract symptoms in BPH, not only functional disorders associated with smooth muscle tone play a significant role, but also structural changes in the prostate and bladder [16, 17], which also reduces the significance of using only PK indicators.

In our cohort, circulating levels of miR-27b did not differ between CYP3A4*22 genotypic groups (CC *vs* CT) and did not correlate with either clinical dynamics on IPSS (dIPSS1-4) or silodosin exposure (Css). This negative result may reflect several factors at once. Firstly, the association of miR-27b with CYP3A4 activity/expression, demonstrated earlier (association with 4β-hydroxycholesterol in vivo and with hepatic CYP3A activity in biopsy samples), has a moderate effect size and manifests itself under direct assessment of hepatic expression (tissue specificity, through concomitant regulatory axes — *VDR / PPAR*α) [12]. Whereas the circulating level of miR-27b may reflect the combined effect of many biological processes not always directly related to the activity of the enzyme in the liver, therefore it is not necessarily reproduced at the level of circulating microRNA in clinical samples with a different profile of concomitant factors. It should be noted that for miR-27b there are studies confirming the existence of a relationship between *CYP3A4* activity (calculated through the ratio of 6-beta-hydroxycortisol

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DOI: 10.19163/2307-9266-2025-13-6-487-499

to cortisol in urine) and the concentration of the drug (rs = -0.27, p = 0.006), metabolized through CYP3A4 (rs = 0.28, p = 0.003) [18]. Such data are presented inconsistently, and the results depend on the study design/cohort size [19]. Secondly, circulating microRNAs are biomarkers with high sensitivity to preanalytical and analytical variations (type of biomaterial and its processing, the effect of hemolysis, normalization strategy), which may reduce the identification of weak associations. The need for strict control and combined normalization (for example, spike-in cel-miR-39 together with endogenous references) is emphasized in modern methodological reviews [20, 21]. Thirdly, the PK of silodosin is determined not only by *CYP3A4*: the CYP3A4 enzyme plays a leading role in the oxidative metabolism of silodosin, but in addition to it, *CYP3A5*, *UGT2B7* conjugation, as well as ABCB1/P-gp transport and redox pathways through ALDH / ADH[3] [22] are involved in the ADME process. All these features can "blur" the expected contribution of *CYP3A4* and the relationship between a single regulator (miR-27b) and the exposure / clinical effect of the drug.

The structure of the identified AEs corresponded to the known safety profile of silodosin: the largest proportion was accounted for by symptoms from the sexual function (retrograde ejaculation) and ENT complaints (rhinitis), while hemodynamic AEs (orthostatic hypotension, dizziness) were less common. These observations reproduce the data of randomized studies, where silodosin consistently shows a high frequency of ejaculation disorders with a relatively low frequency of clinically significant hypotension, which is associated with high selectivity for α1A-adrenoreceptors [23–25]. At the level of subgroups by CYP3A4*22, our work noted heterogeneity in the distribution of individual AEs (a large proportion of orthostatic hypotension and headache in the CT subgroup), which may indirectly indicate the identified increased exposure to silodosin in carriers of the T allele. At the same time, the small number of events in the CT subgroup (n = 12) does not allow us to draw conclusions about the genetically determined risk of AEs.

[3] DrugBank. Silodosin (DB06207); 2025. Available from: https://go.drugbank.com/drugs/DB06207

Study limitations

This study has several limitations. Firstly, the sample size was limited, which, given the prevalence of CYP3A4*22 in the European population at the level of up to 5%, reduces the power and complicates the analysis of associations with the frequency of individual AEs. Secondly, the observational design and relatively short period of therapy (8 weeks) do not allow us to assess long-term outcomes and the long-term safety profile of silodosin. Thirdly, the assessment of miR-27b expression was carried out only in blood plasma. Finally, the influence of concomitant therapy and other clinical factors potentially modulating the exposure and effect of silodosin were not evaluated in this study.

CONCLUSION

Thus, this study demonstrated the effect of genetic polymorphism of the CYP3A4*22 gene on increasing the exposure of silodosin in patients with BPH, while the clinical efficacy of therapy in terms of IPSS and QoL dynamics remained comparable regardless of marker carriage. Circulating miR-27b levels did not demonstrate a relationship with either PK or clinical response, indicating the limited value of this biomarker in the population under consideration. Adverse events corresponded to the known safety profile of silodosin and did not depend on the CYP3A4*22 genotype. Further studies with expanded cohorts are needed to clarify the contribution of both genetic and epigenetic factors to the variability of response to therapy.

FUNDING

The work was supported by the Russian Science Foundation grant (project No. 23-15-00310; https://rscf.ru/project/23-15-00310/).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Shokhrukh P. Abdullaev — investigation, systematization of literature data, writing and editing a draft of the manuscript; Irina V. Bure — investigation, writing—review & editing; Maksim N. Shatokhin — writing—review & editing; Sherzod P. Abdullaev — formal analysis, validation, writing—review & editing;

Pavel O. Bochkov — investigation, formal analysis; Svetlana N. Tuchkova — investigation, formal analysis; Karin B. Mirzaev — conceptualization, writing—review & editing; Oleg B. Loran — writing—review & editing; Dmitry A. Sychev — conceptualization, writing—review & editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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