

1 Article

2 Genetic Modulation of Silodosin Exposure and Efficacy: The 3 Role of CYP3A4, CYP3A5 and UGT2B7 Polymorphisms in Be- 4 nign Prostatic Hyperplasia Management

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Abstract

Objectives: Silodosin, a selective α 1A-adrenoceptor antagonist, is used to treat lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). Genetic polymorphisms in drug-metabolizing enzymes and transporters may contribute to inter-individual variability in its efficacy and safety. This study aimed to investigate the influence of CYP3A4, CYP3A5, UGT2B7, and ABCB1 polymorphisms on silodosin pharmacokinetics, efficacy, and safety in Russian patients with BPH. **Methods:** A prospective observational study included 103 Russian male patients with moderate-to-severe LUTS (IPSS > 8) due to BPH, treated with silodosin (4 mg daily) for 8 weeks. Genotyping for CYP3A4*1B, CYP3A4*22, CYP3A5*3, UGT2B7 (rs73823859, rs7439366, rs7668282), and ABCB1 (rs4148738, rs1045642, rs2032582, rs1128503) was performed using real-time PCR. Silodosin minimum steady-state plasma concentration (C_{ss} min) was measured via HPLC-MS. Efficacy was evaluated by IPSS, quality of life (QoL), maximum urinary flow rate (Q_{max}), residual urine volume, and prostate volume at baseline and week 8. Adverse drug reactions (ADRs) were recorded. **Results:** CYP3A4*22 CT carriers (n=6) exhibited higher C_{ss} min (17.59 ± 2.98 vs. 9.0 ± 10.47 ng/mL, p=0.049) but less absolute IPSS improvement (p<0.05), likely due to higher baseline symptom severity. However, the change in IPSS (Δ IPSS₁₋₄) from baseline to week 8 did not differ significantly (-5.78 ± 5.29 vs. -6.0 ± 4.54, p=0.939). CYP3A53 GG homozygotes (n=96) showed greater Δ IPSS₁₋₄ improvement (-6.25 ± 4.60 vs. 0.0 ± 9.53, p=0.042) and lower IPSS at day 28 (7.64 vs. 20.0, p<0.001). UGT2B7 rs7439366 TT carriers (n=34) had improved Q_{max} (Δ Q_{max}₁₋₄ 5.4 vs. 3.3 and 2.0 mL/s for CC and CT, p=0.047). ABCB1 1236C>T TT homozygotes (n=25) showed a trend toward reduced residual urine volume (p=0.053). No polymorphisms were associated with ADRs (15 events in 42 patients, 35.7%). **Conclusions:** Genetic polymorphisms CYP3A4*22, CYP3A5*3, and UGT2B7 rs7439366 may modulate silodosin pharmacokinetics and efficacy parameters in BPH patients, but not safety. Larger-scale studies are warranted to validate these initial findings.

Keywords: silodosin; pharmacokinetics; polymorphism; UGT2B7; CYP3A4; CYP3A5; ABCB1; benign prostatic hyperplasia; pharmacogenetics.

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1. Introduction

Benign prostatic hyperplasia (BPH) is a non-malignant condition of the prostate characterized histologically by an increase in glandular epithelial tissue, smooth muscle, and connective tissue in the transitional zone of the prostate [1, 2]. A meta-analysis incorporating data from 25 countries reported a lifetime prevalence of BPH of 26.2% (95% CI: 22.8–29.6%) [3]. Global incidence and prevalence rates are projected to rise from 962.42 and 7878.68 per 100,000 population in 2022 to 998.55 and 8620.60 per 100,000 population by 2035, respectively [4]. According to 2019 estimates based on Medicare costs in the United States, global healthcare expenditures for BPH amount to \$73.8 billion annually [5].

BPH is the primary cause of lower urinary tract symptoms (LUTS), which include frequent or urgent urination, weak urinary stream, difficulty initiating urination, nocturia (nighttime urination), and incomplete bladder emptying. If left untreated, BPH can lead to chronic urinary retention with elevated intravesical pressure – a potentially life-threatening condition – and long-term or irreversible changes in the detrusor muscle of the bladder. A recent systematic review and meta-analysis, covering 222 studies from 36 countries, found that the overall prevalence of any LUTS and moderate-to-severe LUTS was 63.2% (95% CI: 58.0–68.1) and 31.3% (95% CI: 28.8–33.8), respectively. The prevalence of LUTS increased from 27.4% (95% CI: 24.5–30.3) in 1990–1999 to 31.9% (95% CI: 27.3–36.7) in 2000–2009, and further to 36.2% (95% CI: 30.7–41.9) in 2010–2019 [6].

Current clinical guidelines from the European Association of Urology (EAU) and the American Urological Association (AUA) recommend selective α 1-adrenoreceptor blockers (ABs) as first-line therapy for alleviating LUTS associated with BPH [7, 8]. Tamsulosin and silodosin are preferred over other α 1-blockers for BPH treatment, primarily due to their high selectivity for the α 1A-adrenoreceptor subtype, which is predominantly located in the prostate and urethra. This urospecificity results in effective relief of LUTS with fewer systemic adverse effects associated with the blockade of α 1B and α 1D receptors, such as orthostatic hypotension. However, 30–40% of patients experience suboptimal symptom improvement, defined as a reduction in the International Prostate Symptom Score (IPSS) of less than 30% or an improvement of fewer than 3 points on the IPSS scale following treatment initiation [4, 9, 10]. Factors contributing to suboptimal response include: a high baseline severity of LUTS (IPSS > 20), which reduces the likelihood of significant improvement; a larger prostate volume (> 40 mL), which often correlates with less symptom improvement with ABs alone; and elderly age or comorbidities, which may influence symptom perception [11]. Safety concerns with ABs also remain a challenge. Common adverse drug reactions (ADRs) associated with tamsulosin and silodosin include dizziness, orthostatic hypotension, ejaculatory dysfunction, and asthenia. This class of drugs is associated with a modest but significant increase in the risk of falls (odds ratio [OR]: 1.14; 95% CI: 1.07–1.21) and fractures (OR: 1.16; 95% CI: 1.04–1.29) [12]. The higher selectivity of silodosin for α 1A-receptors in the lower urinary tract reduces the risk of cardiovascular adverse effects but increases the risk of ejaculatory dysfunction [13, 14]. Age, comorbidities, and concomitant therapies may further influence the safety profile of ABs. The frequency and severity of ADRs vary among individuals, likely due to differences in receptor subtype distribution and variability in drug pharmacokinetics.

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Another factor contributing to the variability in the efficacy and safety of ABs is the genetic profile of patients. Although pharmacogenomic studies analyzing genetic polymorphisms affecting the safety profile of tamsulosin and silodosin are limited [15–18], it is evident that variability in drug-metabolizing enzymes, such as the cytochrome P450 (CYP450) system, contributes to interindividual differences in pharmacological response. The metabolism of ABs is mediated by the enzymes CYP3A4 and CYP2D6, and their genetic polymorphic variants can influence plasma drug levels and, consequently, the risk of toxicity. The CYP3A enzyme family exhibits broad substrate specificity and is involved in the metabolism of over 50% of pharmaceutical drugs [19]. CYP3A4 is considered the dominant isoform within the CYP3A family. Silodosin undergoes metabolism via direct glucuronide conjugation mediated by UDP-glucuronosyltransferase 2B7 (UGT2B7), with CYP3A4 catalyzing its oxidative reactions. In contrast, tamsulosin is primarily metabolized by CYP3A4 and CYP2D6 [20].

Our previous studies involving patients with LUTS/BPH treated with tamsulosin demonstrated that carriage of CYP2D6 allelic variants, specifically *10 and *41, is associated with greater improvement in LUTS and a reduction in residual urine volume. Patients classified as “CYP2D6 intermediate metabolizers” exhibited a better therapeutic response [21, 22]. Carriers of the CYP2D6 *10/*10 or *5/*10 genotypes showed higher plasma concentrations of tamsulosin, which may enhance the drug’s efficacy but is also associated with a more pronounced reduction in blood pressure [15]. In contrast, CYP3A4 and CYP3A5 variants did not influence the efficacy or safety outcomes of tamsulosin therapy in BPH patients [23]. No similar studies have been conducted for silodosin in patients with LUTS due to BPH.

Thus, the aim of this study was to investigate the influence of polymorphisms in the drug-metabolizing enzyme genes CYP3A4, CYP3A5, and UGT2B7, as well as the P-glycoprotein transporter gene (ABCB1), on the efficacy, safety, and pharmacokinetics of silodosin in patients with LUTS/BPH.

2. Materials and Methods

The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee of the Federal State Budgetary Institution of Additional Professional Education “Russian Medical Academy of Continuous Professional Education” of the Ministry of Health of the Russian Federation (RMACPE) (Protocol No. 13, dated December 27, 2021).

Study Design: This was a prospective observational study conducted from October 15, 2023, to May 30, 2025. The study included patients receiving outpatient treatment at the Department of Endoscopic Urology of the RMACPE. Prior to enrollment, each patient provided written informed consent (IC) for participation in the study.

All participants provided written informed consent, which included permission to use anonymized data for scientific publications. The present work contains no personal data that could allow identification of patients.

Inclusion Criteria were as follows: signed IC; a confirmed diagnosis of BPH (ICD-10 code: N40); complaints of moderate-to-severe LUTS, as assessed by an International Prostate Symptom Score (IPSS) > 8 points; and a prostate-specific antigen (PSA) level < 4 ng/mL.

Non-inclusion Criteria included: complicated course of BPH; any conditions other than BPH that, in the doctor’s opinion, could cause dysuria or alter urinary flow rate (e.g., neurogenic bladder, bladder neck sclerosis, urethral stricture, acute or chronic prostatitis, acute or chronic urinary tract infections); concurrent oncological diseases; severe concomitant cardiovascular conditions (e.g., unstable angina, recent myocardial infarction, or poorly controlled arterial hypertension) and cerebrovascular diseases (e.g., recent stroke or spinal cord injuries); and renal or hepatic insufficiency.

Exclusion criteria were: the presence of any contraindications to the use of silodosin; patient refusal to adhere to the prescribed pharmacotherapy; and patient withdrawal of consent to participate in the study.

The study included 103 male patients with complaints of LUTS and a confirmed diagnosis of BPH. Patients were prescribed silodosin at a dose of 4 mg daily, as indicated. Treatment with silodosin commenced at the time of the patient’s initial visit, with follow-up continuing for at least 8 weeks. Treatment was prescribed in accordance with national clinical guidelines for the management of patients with BPH.

On the day of enrollment, 4 mL of blood was collected from each patient into sterile disposable vacuum tubes containing EDTA for subsequent genotyping. Blood sampling was performed concurrently with routine laboratory tests, eliminating the need for additional venipunctures. The biological material was frozen at -20°C, transported to the laboratory, and subsequently stored at -70°C.

The laboratory component of the study was conducted at the Research Institute of Molecular and Personalized Medicine of the RMACPE. For all patients enrolled in the study, real-time polymerase chain reaction (PCR) was used to determine the carriage of polymorphic markers CYP3A4*1B (c.-392G>A, rs2740574), CYP3A4*22 (c.522-191C>T, rs35599367), CYP3A5*3 (A6986G, rs776746), UGT2B7 (rs73823859, rs7439366, rs7668282), and ABCB1 (rs4148738, rs1045642, rs2032582, rs1128503).

For all patients, the minimum steady-state plasma concentration (C_{ss} min) of silodosin was determined. Plasma samples were collected no earlier than 5 days after the initiation of silodosin treatment. The C_{ss} min of silodosin was measured using high-performance liquid chromatography on an Agilent 1200 liquid chromatograph (Agilent Technologies Inc., USA, 2008). Sample preparation was performed using the protein precipitation method. Detection of silodosin spectra was conducted using an Agilent Triple Quad LC/MS 6410 mass spectrometer with electrospray ionization in positive ion mode.

The efficacy of silodosin therapy was evaluated using a combination of clinical and instrumental methods. Clinical assessment included the evaluation of LUTS using the IPSS questionnaire. Instrumental assessments comprised the measurement of maximum urinary flow rate (Qmax), residual urine volume (RUV), and prostate volume (PV) determined by ultrasound. IPSS evaluations were conducted on days 1, 14, 28, and 56 of treatment and follow-up. Instrumental assessments of treatment efficacy were performed on days 1 and 56 of silodosin therapy.

Statistical Analysis: Data were analyzed using parametric and non-parametric statistical methods with the STATISTICA v10.0 software package (StatSoft Inc., USA). The choice of statistical method was based on the normality of data distribution, which was assessed using the Shapiro-Wilk W-test and the Kolmogorov-Smirnov test. For non-normally distributed parameters, descriptive statistics were reported as the median (Me) and interquartile range (25th and 75th percentiles, Q1 and Q3). For normally distributed parameters, descriptive statistics were presented as the mean (M) with standard deviation (SD). Normally distributed data were compared using Student's t-test for paired or unpaired groups. Frequency characteristics of categorical variables were compared using Pearson's χ^2 test. Comparisons between two independent groups were performed using the Mann-Whitney U test, while three or more groups were compared using the Kruskal-Wallis rank analysis of variance, followed by pairwise comparisons with the Mann-Whitney U test and Bonferroni correction for p-value adjustment. A significance level of $p < 0.05$ was considered statistically significant.

3. Results

A total of 103 male patients with BPH and LUTS were included in the study (median age: 69.5 years [64; 76], BMI: 28.72 kg/m² [26.99; 31.49]). The majority of patients had comorbidities, including hypertension (95.2%), ischemic heart disease (47.6%), type 2 diabetes mellitus (16.7%), and urological conditions (23.8%). Common concomitant therapies included CYP3A4 substrates (amlodipine, atorvastatin, losartan, nifedipine). Detailed clinical and demographic characteristics are presented in Table 1.

Table 1. Clinical and Demographic Characteristics of Patients Included in the Study

Parameters	Overall Patient Cohort (n=103)
Age, years	69.5 [64;76]
BMI, kg/m ²	28.72 [26.99; 31.49]
Smoking (n)	11
Alcohol (n)	7
Laboratory Parameters at Baseline	
Creatinine, mmol/L	91.0 [81.0; 103.0]
Urea, mmol/L	5.95 [4.8; 6.9]
Relative density, g/L	1019.5 [1015.0; 1025.0]
pH	6.0 [5.5; 6.0]
Hemoglobin, g/L	148.5 [145.0; 155.0]
Red blood cells, 10 ⁹ /L	4.83 [4.64; 5.2]
White blood cells, 10 ⁹ /L	6.27 [5.56; 6.99]
Platelets, 10 ⁹ /L	222.0 [180.0; 262.0]
Erythrocyte Sedimentation Rate, mm/hour	5.0 [4.0; 9.0]
Prostate-specific antigen, ng/ml	1.89 [0.86; 3.36]
Co-morbidities, n (%)	
Cardiovascular:	65 (63.11%)
Hypertension	40 (38.83%)
Ischemic heart disease	20 (19.42%)

Others	5 (4.85%)	
Endocrine:	9 (8.74%)	
Type 2 diabetes mellitus – insulin-independent	7 (6.80%)	
Hypothyroidis	2 (1.9%)	
Pulmonary:	2 (1.94%)	
Chronic obstructive pulmonary disease	1 (0.97%)	
Bronchial asthma	1 (0.97%)	
Gastroenterological:	3 (2,9%)	
Gastroesophageal reflux disease	1 (0.97%)	
Hepatic steatosis	2 (1.94%)	
Urological:	10 (9.71%)	
Urolithiasis	3 (2.91%)	
Renal cyst	5 (4.85%)	
Erectile dysfunction	2 (1.94%)	
Neurological:	7 (6.8%)	
Degenerative-dystrophic spinal diseases	3 (2.91%)	
Intervertebral hernias	4 (3.88%)	
Concomitant Medication Therapy, n (%)		
CYP3A4 Inhibitors	Allapinine	1 (0.97%)
	Amiodarone	2 (1.94%)
	Eplerenone	1 (0.97%)
CYP3A4 Inducers	-	-
CYP3A4 Substrates	Amlodipine	31 (30.1%)
	Atorvastatin	19 (18.45%)
	Losartan	30 (29.13%)
	Nifedipine	9 (8.74%)
	Doxylamine	1 (0.97%)

The genotype distribution of the investigated polymorphisms conformed to Hardy-Weinberg equilibrium (HWE) ($p > 0.05$), except for CYP3A5*3 (rs776746, $p = 0.083$) and ABCB1 1236C>T (rs1128503, $p = 0.018$). A high frequency of the CYP3A5*3 allele (**G, 95.2%**) was observed, consistent with patterns in European populations. The CYP3A4*1B (rs2740574, A>G) and CYP3A4*22 (rs35599367, C>T) variants were rare, with minor allele frequencies (MAF) of 1.9% and 2.9%, respectively. The complete genotype distribution of the studied polymorphisms is presented in Table 2.

Table 2. Genotype Distribution of Studied Polymorphisms: Allele Frequencies and Hardy-Weinberg Equilibrium Testing

Allele variants	Genotypes	n (%)	Minor allele frequency, %	χ^2	p-value
CYP3A4*1B (rs2740574, A>G)	AA	99 (96.12)	1.9	0.040	0.980
	AG	4 (3.88)			
	GG	0 (0)			
CYP3A4*22 (rs35599367, C>T)	CC	97 (94.17%)	2.9	0.093	0.955
	CT	6 (5.83%)			
	TT	0 (0)			
CYP3A5*3 (rs776746, A6986G)	AA	1 (0.97%)	96.1	4.971	0.083
	AG	6 (5.83%)			
	GG	96 (93.20%)			
UGT2B7 (rs73823859, C>T)	CC	102 (99.03)	0.5	0.002	0.999
	CT	1 (0.97)			
	TT	0 (0)			

UGT2B7 (rs7439366, C>T)	CC	17 (16.50%)	58.3	0.149	0.928
	CT	52 (50.49%)			
	TT	34 (33.01%)			
UGT2B7 (rs7668282, A>G)	AA	92 (89.32%)	5.3	0.328	0.849
	AG	11 (10.68%)			
	GG	0 (0)			
ABCB1 (rs4148738, C>T)	CC	28 (27.18)	44.2	2.683	0.261
	CT	59 (57.28)			
	TT	16 (15.54)			
ABCB1 (rs1045642, 3435T>C)	TT	45 (43.69%)	35.4	0.791	0.673
	CT	43 (41.75%)			
	CC	15 (14.56%)			
ABCB1 (rs2032582, 2677G>T)	GG	19 (18.45%)	55.3	0.379	0.827
	GT	54 (52.43%)			
	TT	30 (29.12%)			
ABCB1 (rs1128503, 1236C>T)	CC	13 (12.62)	55.8	8.047	0.018
	CT	65 (63.11)			
	TT	25 (24.27)			

The analysis revealed that carriers of the CYP3A4*22 CT genotype (n=6) exhibited significantly higher trough steady-state plasma concentrations (C_{ss min}) of silodosin compared to CC homozygotes (n=97) (17.59 ± 2.98 ng/mL vs. 9.0 ± 10.47 ng/mL, $p = 0.049$). However, CT genotype carriers showed less pronounced improvement in IPSS at all evaluation timepoints (days 14, 28, and 56) versus CC homozygotes (n=36) ($p < 0.05$ for all visits). Baseline IPSS scores were comparable between the CC and CT groups (18.5 ± 7.18 vs. 14.21 ± 4.94 , $p = 0.065$). Notably, the overall change in IPSS (Δ IPSS₁₋₄) and quality of life (Δ QoL₁₋₄) from baseline to day 56 did not differ significantly between groups ($p = 0.939$ and $p = 0.520$, respectively).

Silodosin trough C_{ss min} showed no significant association with polymorphisms in CYP3A4*1B (c.-392G>A, rs2740574), CYP3A5*3 (c.6986A>G, rs776746), UGT2B7 (rs73823859, rs7439366, rs7668282), ABCB1 (rs4148738, rs1045642, rs2032582, rs1128503), and ABCG2 (rs2231142, 421C>A) (all $p > 0.05$; see Table 3).

Table 3. Effects of Genetic Polymorphisms on Silodosin C_{ss} min and IPSS Scores at Baseline, Day 14, Day 28, and Day 56 of Treatment

Marker	Geno- types	n	C _{ss} min, ng/mL	Visits								ΔIPSS ₁₋₄	ΔQoL ₁₋₄
				Visit 1 (Day 1)		Visit 2 (Day 14)		Visit 3 (Day 28)		Visit 4 (Day 56)			
				IPSS, points	QoL, points	IPSS, points	QoL, points	IPSS, points	QoL, points	IPSS, points	QoL, points		
CYP3A4*1B (rs2740574, A>G)	AA	99	9.45	13.85±5.48	4.29±0.64	9.58±4.83	2.92±1.25	8.63±5.61	2.31±1.27	7.31±5.93	1.95±1.49	-5.73±5.21	-2.19±1.43
	AG	4	10.62	12±2.45	4±2.59	5±2.29	3±2.60	4±	3±1.05	3±3.44	2±1.55	-9±4.22	-2±0.61
	p-value		0.914	0.347	0.185	0.232	0.911	0.817	0.358	0.982	0.898	0.289	0.821
CYP3A4*22 (rs35599367, C>T)	CC	97	9	14.21±4.94	4.21±0.52	9.21±4.60	2.78±1.11	7.94±5.38	2.18±1.15	6.55±5.66	1.81±1.39	-5.78±5.29	-2.23±1.44
	CT	6	17.59	18.5±7.18	5.0±1.15	15.0±5.09	4.25±1.70	13.0±4.14	3.5±1.73	11.5±4.65	3.25±1.89	-6.0±4.54	-1.75±1.25
	p-value		0.049*	0.065	0.162	0.047*	0.022*	0.037*	0.045*	0.023*	0.045*	0.939	0.520
CYP3A5*3 (rs776746, A6986G)	AA+AG	7	8.4	21.0±7.21	4.66±1.15	12.67±11.15	2.67±2.51	20.0±6.55	3.33±1.15	11.67±10.21	2.0±1.73	0.0±9.53	-1.0±2.0
	GG	96	9.58	13.25±4.96	4.25±0.59	9.23±4.20	2.94±1.14	7.64±4.50	2.23±1.24	6.87±5.51	1.94±1.48	-6.25±4.60	-2.28±1.35
	p-value		0.770	0.015	0.286	0.239	0.708	0.000066*	0.145	0.178	0.954	0.042*	0.133
UGT2B7 (rs73823859, C>T)	CC	102	9.55	13.80±5.42	4.28±0.63	9.47±4.82	2.92±1.23	8.52±5.59	2.30±1.25	7.21±5.90	1.95±1.48	-5.80±5.17	-2.19±1.41
	CT	1	7.00	17	4	9	3	10	3	9	3	-6	-1
	p-value		0.610	0.370	0.249	0.280	0.889	0.223	0.154	0.803	0.708	0.354	0.346957
UGT2B7 (rs7439366, C>T)	CC	17	10.44	15.0±6.50	4.14±0.37	11.28±5.12	3.14±0.69	8.85±5.08	2.14±1.06	8.42±6.24	2.42±0.97	-6.57±4.50	-1.71±1.11
	CT	52	8.49	13.9±5.55	4.38±0.74	8.71±4.96	2.80±1.53	8.95±6.07	2.61±1.24	7.19±6.05	2.04±1.74	-5.14±6.15	-2.04±1.46
	TT	34	10.57	13.07±4.93	4.21±0.57	9.71±4.54	3.0±0.96	7.71±5.38	1.92±1.32	6.64±5.86	1.57±1.22	-6.42±3.93	-2.64±1.44
	p-value		0.613	0.749	0.617	0.473	0.806	0.809	0.268	0.815	0.429	0.714	0.304
UGT2B7 (rs7668282, A>G)	AA	92	9.56	13.71±5.01	4.23±0.58	9.55±4.40	2.94±1.16	8.44±5.58	2.26±1.26	7.23±5.74	1.94±1.50	-5.73±5.40	-2.15±1.48
	AG	11	8.98	14.75±9.53	4.75±0.95	8.75±8.84	2.75±2.06	9.25±6.5	2.75±1.25	7.0±8.28	2.0±1.41	-6.5±2.38	-2.5±0.57
	p-value		0.869	0.720	0.126	0.755	0.765	0.788	0.468	0.940	0.947	0.782	0.651
ABCB1 (rs4148738, C>T)	CC	28	9.16	12.91±3.26	4.25±0.62	9.08±3.34	3.08±1.08	6.58±4.07	2.0±1.27	6.41±5.9	1.83±1.69	-6.5±5.28	-2.41±1.37
	CT	59	9.53	13.79±5.92	4.33±0.7	10.91±5.58	3.04±1.16	9.58±6.22	2.33±1.27	9.16±7.07	2.20±1.47	-4.62±4.55	-2.12±1.42

ABCB1 (rs1045642, 3435T>C)	TT	16	9.96	15.66±7.08	4.16±0.40	10.0±2.82	3.5±0.54	8.16±5.19	2.83±1.16	6.5±5.0	2.16±1.32	-9.16±6.43	-2.0±1.67
	p-value		0.974	0.609	0.832	0.550	0.645	0.319	0.422	0.416	0.779	0.135	0.800
	CC	45	10.6	13.0±7.77	4.16±0.4	7.83±4.07	2.66±1.03	7.16±4.07	2.83±1.47	5.83±4.26	1.83±1.60	-7.16±6.91	-2.33±1.5
	TC	43	9.35	14.64±6.4	4.35±0.7	11.58±5.18	3.11±1.05	9.52±5.53	2.35±1.05	8.7±5.94	2.11±1.05	-5.94±3.86	-2.23±1.39
	TT	15	6.62	13.31±3.55	4.26±0.65	9.84±4.29	3.26±1.09	8.05±6.13	2.1±1.37	8.05±7.61	2.15±1.83	-5.26±5.76	-2.1±1.48
ABCB1 (rs2032582, 2677G>T)	p-value		0.444	0.609	0.832	0.550	0.645	0.319	0.422	0.416	0.779	0.737	0.932
	GG	19	9.03	15.0±6.70	4.14±0.37	9.85±2.60	3.42±0.53	7.85±4.81	2.71±1.11	6.28±4.60	2.14±1.21	-8.71±5.99	-2.0±1.52
	GT	54	9.97	14.0±6.15	4.36±0.72	11.04±5.82	3.09±1.19	9.72±6.46	2.27±1.27	9.45±7.32	2.31±1.46	-4.54±4.75	-2.04±1.43
	TT	30	8.92	12.84±3.13	4.23±0.59	9.15±3.21	3.0±1.08	6.84±4.01	2.15±1.34	6.46±5.65	1.69±1.70	-6.38±5.07	-2.53±1.39
	p-value		0.895	0.689	0.687	0.512	0.690	0.326	0.635	0.322	0.497	0.160	0.577
ABCB1 (rs1128503, 1236C>T)	CC	13	9.75	15.0±6.70	4.14±0.37	9.85±2.60	3.42±0.53	7.85±4.81	2.71±1.11	6.28±4.60	2.14±1.21	-9.0±7.17	-1.4±0.89
	TC	65	9.36	13.61±5.72	4.34±0.68	10.76±5.38	3.03±1.11	9.19±6.13	2.26±1.22	8.73±6.97	2.07±1.49	-4.88±4.5	-2.26±1.48
	TT	25	9.71	13.09±3.36	4.27±0.64	9.09±3.50	3.09±1.13	6.72±4.24	2.0±1.34	6.54±6.17	1.9±1.75	-6.54±5.53	-2.36±1.43
	p-value		0.993	0.516	0.546	0.622	0.566	0.473	0.205	0.642	0.699	0.232	0.417

Note: Δ IPSS₁₋₄ represents changes in IPSS scores relative to baseline until day 56; Δ QoL₁₋₄ indicates changes in quality of life subscale (QoL) scores relative to baseline until day 56; * Statistically significant p-values were observed.



Patients with the CYP3A5*3 GG genotype (n=96) showed significantly greater improvement in IPSS scores by treatment day 56 ($\Delta\text{IPSS}_{1-4} = -6.25 \pm 4.60$) compared to those carrying the A allele (AA+AG genotypes, n=7; $\Delta\text{IPSS}_{1-4} = 0.0 \pm 9.53$, $p=0.042$). At the day 28 assessment, GG carriers maintained superior clinical outcomes (IPSS 7.64 ± 4.50 versus 20.0 ± 6.55 in A-allele carriers; $p < 0.001$). QoL measures did not differ significantly between groups ($p > 0.05$).

No statistically significant differences were observed in IPSS and QoL efficacy outcomes among patients with different ABCB1 (P-glycoprotein) genotypes. However, for the 3435T>C polymorphism, a trend toward greater IPSS improvement was noted in TT homozygotes (n=16, $\Delta\text{IPSS}_{1-4} = -9.16 \pm 6.43$) compared to CT heterozygotes (n=59, $\Delta\text{IPSS}_{1-4} = -4.62 \pm 4.55$) and CC homozygotes (n=6, $\Delta\text{IPSS}_{1-4} = -6.5 \pm 5.28$), though these differences did not reach statistical significance ($p=0.135$).

Analysis of genetic polymorphisms' effects on urodynamic parameters (Table 4) revealed limited but statistically significant associations. Patients with the UGT2B7 (rs7439366) TT genotype (n=34) demonstrated significantly greater improvement in maximum urinary flow rate (Q_{max}) by day 56 of treatment compared to CC and CT genotypes (median Q_{max}: 12.75 mL/s [10.1;14.0] vs. 12.5 [10.1;27.6] and 11.0 [0.0;30.0], respectively; $p=0.044$). The $\Delta\text{Q}_{\text{max}1-4}$ change in TT genotype carriers was -5.4 mL/s [-4.1; -0.9] versus -3.3 [-11.0; -0.8] in CC and -2.0 [-3.0; 0.7] in CT carriers ($p=0.047$).

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Table 4. Impact of Studied Polymorphisms on Urodynamic Parameters (Prostate volume, residual urine volume and Qmax)

Marker	Genotype	n	Visits						ΔRUV ₁₋₄	ΔQ _{max1-4}
			Visit 1 (Day 1)			Visit 4 (Day 56)				
			PV, cm ³	RUV, ml	Q _{max} , ml/sec	PV, cm ³	RUV, ml	Q _{max} , ml/sec		
CYP3A4*1B (rs2740574, A>G)	AA	99	37.2 [31.1;45.3]	14.0 [6.0;33.0]	9.3 [8.1;11.4]	36.5 [31.2;46.0]	13.0 [3.0;25.0]	11.2 [9.2;13.5]	0.0 [-10.0;13.0]	2.4 [-4.8; -0.8]
	AG	4	45.2 [37.65;53.5]	32.5 [15.0;5.0]	9.05 [7.7;10.0]	39.7 [28.6;54.3]	20.0 [7.5;51.5]	11.25 [9.25;15.9]	2.5 [-6.5;12.5]	2.2 [-5.9; -1.55]
	p-value		0.804	0.398	0.695	0.858	0.657	0.289	0.706	0.865
CYP3A4*22 (rs35599367, C>T)	CC	97	36.6 [31.1;47.2]	12.0 [31.2;46.0]	9.35 [7.8;11.4]	36.25 [31.2;46.0]	12.75 [6.0;30.0]	12.1 [9.1;14.0]	0.0 [-8.0;13.0]	2.55 [-4.8; -0.8]
	CT	6	38.75 [32.3;50.45]	27.0 [7.0;52.5]	8.15 [8.1;10.0]	39.5 [32.35;50.5]	20.0 [5.0;54.0]	10.1 [9.15;10.65]	0.0 [-11.5;12.0]	2.0 [2.5; 0.8]
	p-value		0.863	0.453	0.622	0.592	0.715	0.293	0.830	0.492
CYP3A5*3 (rs776746, A6986G)	AA+AG	7	75.9 [26.3;95.3]	30.0 [6.0;40.0]	9.9 [8.1;14.3]	89.7 [26.3;105.0]	10.0 [0.0;30.0]	10.8 [10.1;14.0]	10.0 [6.0;20.0]	0.9 [-2.0; 0.3]
	GG	96	37.2 [31.1;45.3]	13.0 [5.0;33.0]	9.2 [7.8;11.4]	36.5 [31.2;45.0]	13.3 [3.0;25.0]	11.2 [8.8;13.5]	0.0 [-10.0; -13.0]	2.7 [-5.9; 0.8]
	p-value		0.305	0.557	0.574	0.241	0.660	0.769	0.187	0.222
UGT2B7 (rs73823859, C>T)	CC	102	37.25 [31.1;47.2]	13.5 [6.0;33.0]	9.25 [8.0;11.4]	36.75 [31.2;46.0]	12.75 [6.0;33.0]	11.0 [9.1;13.5]	0.0 [-10.0;13.0]	2.2 [-4.8; -0.8]
	CT	1	37	14	9	36	14	10	0.0	1.0
	p-value		0.847	0.363	0.592	0.999	0.702	0.289	0.962	0.878
UGT2B7 (rs7439366, 802 C>T)	CC	17	31.1 [21.4;39.2]	14.0 [0.0;20.0]	9.3 [9.0;15.8]	30.0 [27.0;40.6]	15.0 [0.0;30.0]	12.5 [10.1;27.6]	0.0 [-10.0;13.0]	3.3 [-11.0; -0.8]
	CT	52	37.3 [33.4;45.3]	7.5 [0.0;35.0]	9.4 [7.6;11.4]	37.3 [33.0;44.0]	11.0 [0.0;33.0]	11.0 [0.0;30.0]	0.0 [-10.0;10.0]	2.0 [-3.0;0.7]
	TT	34	44.05 [34.0;61.7]	22.5 [10.0;35.0]	6.5 [-8.0;20.0]	41.0 [32.0;49.2]	12.75 [10.0;25.0]	12.75 [10.1;14.0]	6.5 [-8.0;20.0]	5.4 [-4.1; -0.9]
	p-value		0.089	0.638	0.163	0.213	0.679	0.043*	0.527	0.047*
UGT2B7 (rs7668282, A>G)	AA	92	37.8 [31.5;47.2]	14.5 [6.0;33.0]	9.35 [7.8;11.4]	36.75 [31.2;46.0]	14.0 [3.0;25.0]	10.5 [8.8;13.5]	0.0 [-10.0;14.0]	2.0 [-4.8; -0.7]
	AG	11	33.85 [28.4;43.35]	3.0 [0.0;23.0]	8.9 [8.35;9.5]	33.85 [28.0;42.65]	7.5 [2.5;20.0]	7.5 [2.5;20.0]	0.5 [-5.0;5.5]	3.15 [-6.8; -2.5]

		p-value	0.506595	0.238666	0.699767	0.592232	0.440547	0.324373	0.897718	0.238666
ABCB1 (rs4148738, C>T)	CC	28	42.4 [32.6;48.35]	15.0 [6.75;32.5]	9.0 [8.0;11.45]	37.3 [31.2;45.0]	11.75 [7.5;27.5]	10.95 [8.6;15.65]	0.5 [-7.15;7.5]	1.3 [-7.2; -0.6]
	CT	59	37.25 [32.15;46.15]	12.5 [6.0;31.5]	9.4 [8.05;11.5]	36.25 [29.5;46.7]	11.5 [1.0;23.5]	11.0 [9.7;13.75]	5.5 [-9.0;17.0]	2.85 [-5.35; -0.85]
	TT	16	33.35 [30.5;45.3]	6.5 [0.0;64.0]	8.65 [7.4;10.0]	35.05 [29.7;48.2]	42.5 [0.0;78.5]	11.25 [8.7;12.5]	-1.0 [-13.0;0.0]	2.2 [-3.33; -1.3]
	p-value		0.808	0.420	0.623	0.863	0.057	0.651	0.369	0.310
ABCB1 (rs1045642, 3435T>C)	CC	15	33.85 [27.6;45.1]	0.0 [0.0;10.0]	9.9 [9.2;10.0]	27.85 [25.4;38.0]	6.0 [0.0;25.0]	12.65 [12.4;13.5]	0.0 [-10.0;5.0]	2.9 [-3.3; -2.4]
	TC	43	38.3 [34.0;61.7]	30.0 [9.0;40.0]	8.6 [8.1;9.9]	37.5 [34.0;53.1]	15.0 [10.0;35.0]	10.2 [10.1;13.4]	0.0 [-5.0;20.0]	2.0 [-5.9; -0.9]
	TT	45	35.2 [29.1;47.2]	11.0 [6.0;30.0]	9.4 [7.7;11.8]	36.5 [31.2;44.0]	11.0 [5.0;25.0]	10.1 [8.4;14.0]	1.0 [-10.0;11.0]	1.5 [-4.8; 0.3]
	p-value		0.168	0.060	0.548	0.116	0.813	0.950	0.253	0.764
ABCB1 (rs2032582, 2677G>T)	GG	19	35.2 [30.5;61.7]	13.0 [0.0;65.0]	8.6 [7.4;10.0]	37.5 [29.7;48.4]	15.0 [0.0;78.0]	12.4 [8.7;12.7]	0.0 [-13.0;22.0]	2.4 [-4.1; -1.3]
	GT	54	36.6 [31.1;44.3]	10.5 [6.0;30.0]	9.4 [8.0;11.4]	36.25 [32.0;45.0]	10.0 [0.0;22.0]	10.5 [9.5;13.5]	3.0 [-10.0;14.0]	2.75 [-4.8; -0.8]
	TT	30	43.8 [35.0;47.2]	15.0 [7.5;30.0]	9.4 [8.3;11.4]	37.0 [31.2;44.0]	12.5 [10.0;25.0]	11.8 [8.8;18.9]	1.0 [-4.3;5.0]	1.5 [-9.4; -0.7]
	p-value		0.969	0.292	0.561	0.602	0.114	0.834	0.616	0.876
ABCB1 (rs1128503, 1236C>T)	CC	13	31.5 [30.5;45.3]	15.0 [6.0;30.0]	9.2 [8.1;10.0]	32.6 [29.7;48.2]	12.0 [5.0;30.0]	12.4 [10.1;12.5]	-0.5 [-7.15;7.5]	2.4 [-3.3; -2.0]
	TC	65	36.6 [31.1;44.3]	10.5 [6.0;30.0]	9.4 [8.0;11.4]	36.25 [32.0;45.0]	10.0 [0.0;22.0]	10.5 [9.5;13.5]	3.0 [-10.0;14.0]	2.75 [-4.8; -0.8]
	TT	25	43.8 [35.0;49.5]	15.0 [0.0;13.0]	9.4 [8.3;11.5]	37.6 [31.2;46.0]	9.0 [0.0;30.0]	11.8 [8.8;18.9]	-1.0 [-10.0;5.0]	1.5 [-10.3; -0.5]
	p-value		0.860	0.704	0.794	0.825	0.405	0.794	0.053	0.869

Note: PV – prostate volume; RUV – residual urine volume; Qmax – maximum urinary flow rate; ΔRV_{1-4} – change in RUV from baseline to day 56; ΔQ_{max1-4} – change in Qmax from baseline to day 56; * Statistically significant p-values were observed.



For the ABCB1 1236C>T variant, a trend toward reduced residual urine volume (ΔRUV_{1-4}) was observed in TT homozygotes ($n=25$): -1.0 [$-10.0;5.0$] mL versus 0.5 [$-7.15;7.5$] in CC and 3.0 [$-10.0;14.0$] in CT genotypes ($p=0.053$). The polymorphisms CYP3A4*1B, CYP3A4*22, CYP3A5*3, UGT2B7 (rs73823859, rs7668282), and ABCB1 (rs4148738, rs1045642, rs2032582) showed no significant effect on RUV, Qmax, or prostate volume (PV) dynamics ($p>0.05$ for all comparisons). The absence of PV changes across all groups (median ΔPV_{1-4} range: -1.0 to $+6.5$ cm³) confirms that silodosin does not affect the morphological component of BPH.

Interestingly, for CYP3A4*22 (CT genotype) - despite its association with differences in C_{ss} min and clinical response - no correlation was found with urodynamic parameters ($p=0.222$ for ΔRUV_{1-4} and $p=0.493$ for ΔQ_{max1-4} , respectively). This finding highlights the complex relationship between genetic factors, drug concentration, and functional outcomes in BPH treatment.

During the observation period, 15 ADRs were recorded in 42 patients (35.7%). ADRs included: rhinitis ($n=5$, 33.3%), orthostatic hypotension ($n=4$, 26.6%), retrograde ejaculation ($n=2$, 13.3%), dizziness ($n=2$, 13.3%), diarrhea ($n=1$, 6.6%), and headache ($n=1$, 6.6%). Analysis of polymorphisms' association with ADR incidence revealed no statistically significant correlations for any genetic variants ($p>0.05$ for all). Odds ratios for all analyzed polymorphisms were non-significant.

4. Discussion

This study represents the first comprehensive investigation examining the effects of polymorphisms in CYP3A4*1B (c.-392G>A, rs2740574), CYP3A4*22 (c.522-191C>T, rs35599367), CYP3A5*3 (c.6986A>G, rs776746), UGT2B7 (rs73823859, rs7439366, rs7668282), and ABCB1 (rs4148738, rs1045642, rs2032582, rs1128503) on both the pharmacokinetics and clinical effects of silodosin in BPH patients. The key findings demonstrate that genetic variants of CYP3A4, CYP3A5, and UGT2B7 may contribute to the modulation of pharmacokinetic profiles and therapeutic response, though they showed no association with drug safety.

Silodosin undergoes extensive metabolism primarily via CYP3A4, UDP-glucuronosyltransferase 2B7, and alcohol/aldehyde dehydrogenases. CYP3A4 catalyzes its oxidative metabolism, producing hydroxylated and ketonized derivatives. Predominantly expressed in the liver and intestine, CYP3A4 significantly influences oral bioavailability, systemic clearance, and consequently, the drug's systemic exposure. CYP3A4 activity exhibits substantial interindividual variability due to genetic polymorphisms, environmental factors, health status, and comorbidities. The CYP3A4*18B and CYP3A4*22 variants demonstrate particularly pronounced effects on drug metabolism. While CYP3A4*18B reduces metabolism of some drugs (e.g., requiring lower fentanyl doses for postoperative analgesia in *18B/*18B homozygotes [24]), it increases clearance of others like cyclosporine and tacrolimus [25,26], reflecting substrate-dependent modulation of enzyme activity. This variant predominates in East Asian populations (Chinese, Korean, Japanese) [27,28] but is virtually absent in Caucasians. The CYP3A4*22 variant (rs35599367 C>T), located in intron 6, causes alternative splicing that reduces CYP3A4 expression and activity by 40-50% [29]. With a minor allele frequency of ~5% in Caucasians versus <0.6% in Asians [30], CYP3A4*22 alters clearance and pharmacologic responses of various CYP3A4 substrates - reducing quetiapine [31] and tacrolimus [32] dosing requirements while increasing cyclosporine exposure and toxicity risk [33].

In our study, carriers of the CYP3A422 allele (CT genotype) showed 95% higher trough silodosin concentrations (C_{ss} min: 17.59 vs. 9.0 ng/mL, $p=0.049$), consistent with this variant's known mechanism. As silodosin is a CYP3A4 substrate, reduced metabolic activity predictably increases systemic exposure. Paradoxically, despite higher concentrations, CT genotype patients demonstrated less symptom improvement by absolute IPSS scores ($p<0.05$ at all visits). However, the overall IPSS reduction by day 56 was comparable between CC and CT groups ($\Delta IPSS_{1-4}$: -5.78 ± 5.29 vs. -6.0 ± 4.54 , $p=0.939$), potentially explained by CT group's more severe baseline symptoms (baseline IPSS: 18.5 vs. 14.21). Similarly, QoL assessments showed significant differences at all visits ($p<0.05$), but ΔQoL_{1-4} were comparable between CC and CT groups ($p=0.520$). LUTS reflect both dynamic obstruction (responsive to $\alpha 1$ -blockers) and mechanical obstruction from prostate volume or detrusor changes (less responsive to $\alpha 1$ -blockers). Our data show no significant prostate volume difference between CC and CT groups (38.75 vs. 36.6 cm³, $p=0.86$). Further large-scale studies are necessary to fully assess polymorphism effects on clinical outcomes, especially concerning prostate volume.

The lack of correlation between CYP3A4*22 and changes in ΔRUV_{1-4} or ΔQ_{max1-4} , despite its association with IPSS scores, suggests that genetic factors may differentially influence subjective symptoms versus objective urinary parameters.

Our study included analysis of UGT2B7 variants - the key phase II metabolism enzyme responsible for silodosin glucuronidation. This process converts the lipophilic compound into a water-soluble metabolite (silodosin-glucuronide), facilitating renal and biliary excretion [20]. While UGT2B7 genetic variants can significantly affect enzyme activity, their role in silodosin therapy hadn't been previously examined in clinical cohorts. None of the studied UGT2B7 variants (rs73823859 C>T, rs7439366 C>T, rs7668282 A>G) showed significant associations with silodosin plasma concentrations ($p>0.05$). This contrasts with findings by Wang Z et al (2013) in healthy Chinese volunteers, where UGT2B7*1/*2 and *2/*2 genotypes showed 27.1% and 22.7% longer terminal half-life ($t_{1/2}$) and 37.9% and 25.2% greater $AUC_{0-\infty}$ compared to UGT2B7*1/*1, indicating slower metabolism and increased drug exposure [17]. These discrepancies may be explained by the fact that the frequency of the T allele at rs7439366 (associated with UGT2B7*2) in our Caucasian cohort (58.3%) differs from Asian populations be explained by the fact that the frequency of the T allele at rs7439366 (associated with UGT2B7*2) in our Caucasian cohort (58.3%) differs from Asian populations. Alternatively, the presence of BPH and other comorbidities in our patients may have neutralized the effect of the marker.

Our study revealed that patients homozygous for the UGT2B7 rs7439366 TT genotype ($n=34$) demonstrated significantly greater improvement in maximum urinary flow rate (Q_{max}) by day 56 of treatment compared to CC ($n=17$) and CT ($n=52$) genotypes: 5.4 mL/s versus 3.3 mL/s and 2.0 mL/s, respectively ($p=0.047$). Similarly, absolute Q_{max} values at day 56 were higher in TT carriers: 12.75 mL/s versus 12.5 mL/s (CC) and 11.0 mL/s (CT) ($p=0.044$). The rs73823859 C>T (MAF=0.5%) and rs7668282 A>G (MAF=5.3%) polymorphisms showed no significant associations with either pharmacodynamic or pharmacokinetic parameters of silodosin, which may reflect their lower functional impact or insufficient statistical power in our sample size to detect effects.

The CYP3A5*3 allele (rs776746, A6986G) causes splicing defects resulting in nonfunctional CYP3A5 protein. The CYP3A53 allele frequency varies substantially across populations (24-92%), explaining the observed ethnic variability in CYP3A5 expression. While poor CYP3A4 metabolizers are rare, CYP3A5 nonfunctionality is common in many populations [34]. Individuals carrying at least one CYP3A5*1 allele exhibit CYP3A5 mRNA expression comparable to CYP3A4, potentially significantly influencing overall CYP3A activity [35]. In our study, GG homozygotes (poor metabolizers) showed significantly better symptom improvement ($\Delta IPSS_{1-4}$: -6.25 ± 4.60 vs. 0.0 ± 9.53 in A-allele carriers; $p=0.042$), with

sustained effects at day 28 (IPSS 7.64 vs. 20.0; $p < 0.001$). This aligns with CYP3A5's role as an alternative metabolic pathway - functional CYP3A5 (in A-allele carriers) may increase clearance, reducing drug exposure and efficacy. However, we found no CYP3A5*3 effect on silodosin C_{ss} min. This contradicts previous findings by Wang Z et al. (2013), who showed that in healthy volunteers, the CYP3A5 marker significantly correlated with changes in silodosin T_{max} ($p = 0.039$), with a significantly prolonged time to peak concentration (C_{max}) in individuals with the CYP3A5*1/*1 genotype compared to CYP3A5*1/*3 and *3/*3 carriers [17]. Larger studies are needed to clarify CYP3A5*3's clinical impact in BPH patients.

No significant associations were found between CYP3A4*1B and silodosin efficacy parameters, C_{ss} min concentrations, or safety outcomes. The pharmacogenetic data on CYP3A4*1B remain contradictory. While in vitro studies suggest this variant increases CYP3A activity [36], and clinical studies report its impact on tacrolimus dosing in transplant patients [37, 38], its tight linkage with functional CYP3A5*1 makes it difficult to isolate CYP3A4*1B's independent effects. The clinical relevance of CYP3A4*1B for silodosin response requires further investigation.

P-glycoprotein (P-gp), encoded by the ABCB1 gene, is a transporter protein responsible for cellular efflux of xenobiotics and pharmaceutical compounds. In vitro studies have demonstrated that silodosin is a P-gp substrate [39]. Prescribing information for silodosin contains warnings about drug interactions, noting that coadministration with strong transporter inhibitors (e.g., amiodarone, verapamil) significantly increases drug concentrations [40]. Three major ABCB1 variants - 3435T>C, 2677T>G/A, and 1236T>C - have been extensively studied. These SNPs form haplotypes associated with altered P-gp function, typically resulting in reduced activity and modified substrate specificity [41]. These variants influence pharmacokinetics and clinical outcomes for multiple drug classes including anticoagulants, antineoplastic agents, and proton pump inhibitors [42–44]. The rs4148738 C>T variant affects dabigatran pharmacokinetics [45], while in apixaban-treated patients it correlates with increased bleeding risk [46]. For silodosin, theoretically, reduced P-gp efflux activity in polymorphism carriers could increase drug concentrations in prostate/urethral tissues, potentially enhancing smooth muscle relaxation and bladder emptying. However, our study found no statistically significant effects of 3435T>C, 2677G>T, 1236C>T, or rs4148738 C>T polymorphisms on silodosin's C_{ss} min, efficacy parameters, or safety profile in BPH patients. These findings suggest limited clinical relevance of these genetic variants for silodosin therapy.

A key finding of our study was the absence of statistically significant associations between the investigated genetic polymorphisms (CYP3A4, CYP3A5, UGT2B7, ABCB1) and the frequency or nature of silodosin's ADRs. Despite significantly higher C_{ss} min plasma concentrations in CYP3A4*22 allele carriers (which theoretically could increase dose-dependent effects), no reliable association was found between this marker and systemic ADRs such as orthostatic hypotension or dizziness. Silodosin exhibits exceptionally high selectivity (583-fold greater than tamsulosin) for α 1A-adrenoceptors predominant in prostate, bladder neck, and prostatic urethra smooth muscle, while demonstrating minimal affinity for α 1B (vascular) and α 1D (CNS, myocardial) receptors. This selectivity minimizes systemic effects even with elevated plasma drug exposure. Our data confirm this: orthostatic hypotension occurred in only 4 patients (26.6% of all ADRs) and dizziness in 2 (13.3%). The most frequent ADRs were rhinitis (33.3%) and retrograde ejaculation (13.3%) - consequences of silodosin's local pharmacological action on α 1A-receptors in seminal ducts and nasal mucosa vasculature rather than systemic toxicity. These effects depend on target tissue receptor blockade achieved at therapeutic doses and remain relatively insensitive to moderate increases in systemic concentration. The lack of associations

may partially reflect insufficient power to detect effects of rare alleles (e.g., only 6 patients carried CYP3A4*22) on relatively uncommon or severe ADRs.

Limitations. This study has several important limitations that should be considered when interpreting the results. First, the relatively small sample size (n=103) and low minor allele frequencies of key polymorphisms (CYP3A4*22 [MAF=2.9%, n=6 CT] and CYP3A5*1 [MAF=3.4%, n=7 AA/AG]) limited statistical power to detect moderate effects and perform stratified subgroup analyses. Second, focusing solely on trough plasma concentrations (C_{ss} min) without assessing the complete pharmacokinetic profile (AUC₀₋₄, T_{max}, t_{1/2}) may have underestimated genetic variants' contribution to systemic exposure. Third, the lack of strict dietary control (due to outpatient monitoring condition) and precise documentation of concomitant medication timing (CYP3A4 substrates: amlodipine [30.1%], losartan [29.1%], atorvastatin [18.4%]) may have introduced unaccounted variability in silodosin concentrations. Fourth, the 8-week observation period was sufficient for evaluating symptomatic response but might be insufficient for assessing long-term outcomes (BPH progression, need for surgical intervention) and potential cumulative effects of pharmacogenetic markers on safety. Fifth, the study was conducted exclusively in Caucasian patients, limiting generalizability to other populations.

5. Conclusions

This study demonstrates that genetic polymorphisms CYP3A4*22 (rs35599367) and CYP3A5*3 (rs776746) significantly affect the pharmacokinetics and clinical effects of silodosin in BPH patients: carriers of the CYP3A4*22 allele (CT genotype) had higher C_{ss} min (17.59 ± 2.98 ng/mL versus 9.0 ± 10.47 ng/mL in CC; p=0.049), which correlates with less improvement in absolute IPSS scores at all visits (p<0.05) but not with symptom dynamics (ΔIPSS₁₋₄, p=0.939), likely due to initially more severe symptoms in this subgroup; meanwhile, CYP3A5*3 GG homozygotes showed significantly better IPSS improvement by day 56 (ΔIPSS₁₋₄ -6.25±4.60 versus 0.0±9.53 in AA/AG; p=0.042) and at day 28 (IPSS 7.64 versus 20.0; p<0.001), indicating CYP3A5's role in silodosin metabolism. The UGT2B7 rs7439366 TT variant was associated with better Q_{max} dynamics (ΔQ_{max}₁₋₄ -5.4 mL/s versus -3.3 in CC and -2.0 in CT; p=0.047), highlighting glucuronidation's contribution to urodynamic response. ABCB1 polymorphisms showed no significant associations with drug efficacy or safety in BPH patients. Despite the identified differences, no marker was associated with ADR frequency (15 events in 42 patients; p>0.05), attributable to silodosin's high uroselectivity minimizing systemic effects even at increased exposure.

The studied polymorphisms showed limited clinical significance, with moderate effects. No link was found between genetic variants and adverse reactions, questioning the need for routine pharmacogenetic testing before silodosin use. Further studies are needed in a larger population and ethnic groups to determine the combined effects of SNPs on silodosin pharmacokinetics and to determine the clinical importance of the pharmacogenetic markers in silodosin therapy.

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Data Availability Statement: The datasets generated and analyzed during this study are not publicly available due to ethical restrictions and patient confidentiality protections under Russian Federation laws on personal data protection (Federal Law No. 152-FZ). However, anonymized data supporting the findings may be made available upon reasonable request from qualified researchers, subject to approval by the Ethics Committee of the Russian Medical Academy of Continuous Professional Education (contact: rmanpo@rmapo.ru). Requests should include a detailed research proposal and data protection plan.

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Abbreviations

The following abbreviations are used in this manuscript:

ABCB1	ATP-Binding Cassette Subfamily B Member 1 (P-glycoprotein)
ABs	α 1-Adrenoreceptor Blockers
ADRs	Adverse Drug Reactions
BPH	Benign Prostatic Hyperplasia
Css min	Minimum Steady-State Plasma Concentration
CYP3A4	Cytochrome P450 3A4
CYP3A5	Cytochrome P450 3A5
ICD-10	International Classification of Diseases, 10th Revision
IPSS	International Prostate Symptom Score
MAF	Minor Allele Frequency
P-gp	P-glycoprotein
PSA	Prostate-Specific Antigen
PV	Prostate Volume
Qmax	Maximum Urinary Flow Rate
QoL	Quality of Life of IPSS
RMACPE	Russian Medical Academy of Continuous Professional Education
RUV	Residual Urine Volume
SNP	Single Nucleotide Polymorphism
UGT2B7	UDP-Glucuronosyltransferase 2B7

References

- Chughtai, B., Forde, J. C., Thomas, D. D., Laor, L., Hossack, T., Woo, H. H., Te, A. E., & Kaplan, S. A. (2016). Benign prostatic hyperplasia. *Nature reviews. Disease primers*, 2, 16031. <https://doi.org/10.1038/nrdp.2016.31>
- Sandhu, J. S., Bixler, B. R., Dahm, P., Goueli, R., Kirkby, E., Stoffel, J. T., & Wilt, T. J. (2024). Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia (BPH): AUA Guideline Amendment 2023. *The Journal of urology*, 211(1), 11–19. <https://doi.org/10.1097/JU.0000000000003698>
- Lee, S. W. H., Chan, E. M. C., & Lai, Y. K. (2017). The global burden of lower urinary tract symptoms suggestive of benign prostatic hyperplasia: A systematic review and meta-analysis. *Scientific reports*, 7(1), 7984. <https://doi.org/10.1038/s41598-017-06628-8>
- Wei, H., Zhu, C., Huang, Q. et al. Global, regional, and national burden of benign prostatic hyperplasia from 1990 to 2021 and projection to 2035. *BMC Urol* 25, 34 (2025). <https://doi.org/10.1186/s12894-025-01715-9>
- Devlin, C. M., Simms, M. S., & Maitland, N. J. (2021). Benign prostatic hyperplasia - what do we know?. *BJU international*, 127(4), 389–399. <https://doi.org/10.1111/bju.15229>
- Huang, J., Chan, C. K., Yee, S., Deng, Y., Bai, Y., Chan, S. C., Tin, M. S., Liu, X., Lok, V., Zhang, L., Xu, W., Zheng, Z. J., Teoh, J. Y., Ng, C. F., & Wong, M. C. S. (2023). Global burden and temporal trends of lower urinary tract symptoms: a systematic review and meta-analysis. *Prostate cancer and prostatic diseases*, 26(2), 421–428. <https://doi.org/10.1038/s41391-022-00610-w>
- Lerner, L. B., McVary, K. T., Barry, M. J., Bixler, B. R., Dahm, P., Das, A. K., Gandhi, M. C., Kaplan, S. A., Kohler, T. S., Martin, L., Parsons, J. K., Roehrborn, C. G., Stoffel, J. T., Welliver, C., & Wilt, T. J. (2021). Management of Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: AUA GUIDELINE PART I-Initial Work-up and Medical Management. *The Journal of urology*, 206(4), 806–817. <https://doi.org/10.1097/JU.0000000000002183>
- EAU Guidelines. Edn. presented at the EAU Annual Congress Paris April 2024. ISBN 978-94-92671-23-3
- Ali, M., Landeira, M., Covernton, P. J. O., Choudhury, N., Jaggi, A., Fatoye, F., & van Maanen, R. (2021). The use of mono- and combination drug therapy in men and women with lower urinary tract symptoms (LUTS) in the UK: a retrospective observational study. *BMC urology*, 21(1), 119. <https://doi.org/10.1186/s12894-021-00881-w>
- Brasure M, MacDonald R, Dahm P, et al. Newer Medications for Lower Urinary Tract Symptoms Attributed to Benign Prostatic Hyperplasia: A Review [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2016 May. (Comparative Effectiveness Reviews, No. 178.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK368444/>
- Hong, K. P., Byun, Y. J., Yoon, H., Park, Y. Y., & Chung, W. S. (2010). Prospective factor analysis of alpha blocker monotherapy failure in benign prostatic hyperplasia. *Korean journal of urology*, 51(7), 488–491. <https://doi.org/10.4111/kju.2010.51.7.488>
- Welk, B., McArthur, E., Fraser, L. A., Hayward, J., Dixon, S., Hwang, Y. J., & Ordon, M. (2015). The risk of fall and fracture with the initiation of a prostate-selective α antagonist: a population based cohort study. *BMJ (Clinical research ed.)*, 351, h5398. <https://doi.org/10.1136/bmj.h5398>
- Jung, J. H., Kim, J., MacDonald, R., Reddy, B., Kim, M. H., & Dahm, P. (2017). Silodosin for the treatment of lower urinary tract symptoms in men with benign prostatic hyperplasia. *The Cochrane database of systematic reviews*, 11(11), CD012615. <https://doi.org/10.1002/14651858.CD012615.pub2>
- Silva, J., Silva, C. M., & Cruz, F. (2014). Current medical treatment of lower urinary tract symptoms/BPH: do we have a standard?. *Current opinion in urology*, 24(1), 21–28. <https://doi.org/10.1097/MOU.0000000000000007>
- Kim, K. A., Park, I. B., & Park, J. Y. (2018). Effects of CYP2D6 and CYP3A5 genetic polymorphisms on steady-state pharmacokinetics and hemodynamic effects of tamsulosin in humans. *European journal of clinical pharmacology*, 74(10), 1281–1289. <https://doi.org/10.1007/s00228-018-2501-x>
- Villapalos-García, G., Zubiaur, P., Navares-Gómez, M., Saiz-Rodríguez, M., Mejía-Abril, G., Martín-Vílchez, S., Román, M., Ochoa, D., & Abad-Santos, F. (2021). Effects of Cytochrome P450 and Transporter Polymorphisms on the Bioavailability and Safety of Dutasteride and Tamsulosin. *Frontiers in pharmacology*, 12, 718281. <https://doi.org/10.3389/fphar.2021.718281>
- Wang, Z., Xiang, Q., Cui, Y., Zhao, X., & Zhou, Y. (2013). The influence of UGT2B7, UGT1A8, MDR1, ALDH, ADH, CYP3A4 and CYP3A5 genetic polymorphisms on the pharmacokinetics of silodosin in healthy Chinese volunteers. *Drug metabolism and pharmacokinetics*, 28(3), 239–243. <https://doi.org/10.2133/dmpk.dmpk-12-rg-106>
- Choi C. I., Bae J. W., Jang C. G., Lee S. Y. (2012). Tamsulosin exposure is significantly increased by the CYP2D6*10/*10 genotype. *J. Clin. Pharmacol.* 52, 1934–1938. [10.1177/0091270011432168](https://doi.org/10.1177/0091270011432168)
- Klyushova, L. S., Perepechaeva, M. L., & Grishanova, A. Y. (2022). The Role of CYP3A in Health and Disease. *Biomedicines*, 10(11), 2686. <https://doi.org/10.3390/biomedicines10112686>

20. Knox, C., Wilson, M., Klinger, C. M., Franklin, M., Oler, E., Wilson, A., Pon, A., Cox, J., Chin, N. E. L., Strawbridge, S. A., Garcia-Patino, M., Kruger, R., Sivakumaran, A., Sanford, S., Doshi, R., Khetarpal, N., Fatokun, O., Doucet, D., Zubkowski, A., Rayat, D. Y., ... Wishart, D. S. (2024). DrugBank 6.0: the DrugBank Knowledgebase for 2024. *Nucleic acids research*, 52(D1), D1265–D1275. <https://doi.org/10.1093/nar/gkad976>
21. Abdullaev, S. P., Shatokhin, M. N., Tuchkova, S. N., Abdullaev, S. P., Teodorovich, O. V., Loran, O. B., & Sychev, D. A. (2023). Effects of CYP2D6 allelic variants on therapy with tamsulosin in patients with benign prostatic hyperplasia. *Drug metabolism and personalized therapy*, 38(4), 323–330. <https://doi.org/10.1515/dmpt-2023-0050>
22. Abdullaev, S., Shatokhin, M., Sychev, I., Krasnov, A., Bochkov, P., Tuchkova, S., Teodorovich, O., Loran, O., Abdullaev, S., & Sychev, D. (2025). CYP2D6 genetic polymorphisms impact on tamsulosin efficacy and safety in patients with benign prostatic hyperplasia. *Drug metabolism and personalized therapy*, 40(1), 55–67. <https://doi.org/10.1515/dmpt-2024-0061>
23. Abdullaev, Sh.P., Shatokhin, M.N., Sigailo, O.L., Abdullaev, Sh.P., Bochkov, P.O., Tuchkova, S.N., Teodorovich, O.V., Loran, O.B., Sychev, D.A. (2024). Association of CYP3A4*1B, CYP3A4*22 and CYP3A5*3 polymorphisms carriage with efficacy and safety of tamsulosin in patients with benign prostatic hyperplasia. *Pharmacy & Pharmacology*, 12(1), 32–48. [In Russ.] <https://doi.org/10.19163/2307-9266-2024-12-1-32-48>
24. Liao, Q., Chen, D. J., Zhang, F., Li, L., Hu, R., Tang, Y. Z., Ou-Yang, W., & Huang, D. (2013). Effect of CYP3A4*18B polymorphisms and interactions with OPRM1 A118G on postoperative fentanyl requirements in patients undergoing radical gastrectomy. *Molecular medicine reports*, 7(3), 901–908. <https://doi.org/10.3892/mmr.2013.1270>
25. Li, D. Y., Teng, R. C., Zhu, H. J., & Fang, Y. (2013). CYP3A4/5 polymorphisms affect the blood level of cyclosporine and tacrolimus in Chinese renal transplant recipients. *International journal of clinical pharmacology and therapeutics*, 51(6), 466–474. <https://doi.org/10.5414/CP201836>
26. Liu, F., Ou, Y. M., Yu, A. R., Xiong, L., & Xin, H. W. (2017). Long-Term Influence of CYP3A5, CYP3A4, ABCB1, and NR1I2 Polymorphisms on Tacrolimus Concentration in Chinese Renal Transplant Recipients. *Genetic testing and molecular biomarkers*, 21(11), 663–673. <https://doi.org/10.1089/gtmb.2017.0088>
27. Hu, G. X., Dai, D. P., Wang, H., Huang, X. X., Zhou, X. Y., Cai, J., Chen, H., & Cai, J. P. (2017). Systematic screening for CYP3A4 genetic polymorphisms in a Han Chinese population. *Pharmacogenomics*, 18(4), 369–379. <https://doi.org/10.2217/pgs-2016-0179>
28. Fukushima-Uesaka, H., Saito, Y., Watanabe, H., Shiseki, K., Saeki, M., Nakamura, T., Kurose, K., Sai, K., Komamura, K., Ueno, K., Kamakura, S., Kitakaze, M., Hanai, S., Nakajima, T., Matsumoto, K., Saito, H., Goto, Y., Kimura, H., Katoh, M., Sugai, K., ... Sawada, J. (2004). Haplotypes of CYP3A4 and their close linkage with CYP3A5 haplotypes in a Japanese population. *Human mutation*, 23(1), 100. <https://doi.org/10.1002/humu.9210>
29. Wang, D., & Sadee, W. (2016). CYP3A4 intronic SNP rs35599367 (CYP3A4*22) alters RNA splicing. *Pharmacogenetics and genomics*, 26(1), 40–43. <https://doi.org/10.1097/FPC.0000000000000183>
30. Mulder, T. A. M., van Eerden, R. A. G., de With, M., Elens, L., Hesselink, D. A., Matic, M., Bins, S., Mathijssen, R. H. J., & van Schaik, R. H. N. (2021). CYP3A4*22 Genotyping in Clinical Practice: Ready for Implementation?. *Frontiers in genetics*, 12, 711943. <https://doi.org/10.3389/fgene.2021.711943>
31. Beunk, L., Nijenhuis, M., Soree, B., de Boer-Veger, N. J., Buunk, A. M., Guchelaar, H. J., Houwink, E. J. F., Risselada, A., Rongen, G. A. P. J. M., van Schaik, R. H. N., Swen, J. J., Touw, D., van Westrhenen, R., Deneer, V. H. M., & van der Weide, J. (2024). Dutch Pharmacogenetics Working Group (DPWG) guideline for the gene-drug interaction between CYP2D6, CYP3A4 and CYP1A2 and antipsychotics. *European journal of human genetics : EJHG*, 32(3), 278–285. <https://doi.org/10.1038/s41431-023-01347-3>
32. Elens, L., Bouamar, R., Hesselink, D. A., Haufroid, V., van der Heiden, I. P., van Gelder, T., & van Schaik, R. H. (2011). A new functional CYP3A4 intron 6 polymorphism significantly affects tacrolimus pharmacokinetics in kidney transplant recipients. *Clinical chemistry*, 57(11), 1574–1583. <https://doi.org/10.1373/clinchem.2011.165613>
33. Elens, L., Bouamar, R., Hesselink, D. A., Haufroid, V., van Gelder, T., & van Schaik, R. H. (2012). The new CYP3A4 intron 6 C>T polymorphism (CYP3A4*22) is associated with an increased risk of delayed graft function and worse renal function in cyclosporine-treated kidney transplant patients. *Pharmacogenetics and genomics*, 22(5), 373–380. <https://doi.org/10.1097/FPC.0b013e328351f3c1>
34. Hustert, E., Haberl, M., Burk, O., Wolbold, R., He, Y. Q., Klein, K., Nuessler, A. C., Neuhaus, P., Klattig, J., Eiselt, R., Koch, I., Zibat, A., Brockmöller, J., Halpert, J. R., Zanger, U. M., & Wojnowski, L. (2001). The genetic determinants of the CYP3A5 polymorphism. *Pharmacogenetics*, 11(9), 773–779. <https://doi.org/10.1097/00008571-200112000-00005>

35. Lin, Y. S., Dowling, A. L., Quigley, S. D., Farin, F. M., Zhang, J., Lamba, J., Schuetz, E. G., & Thummel, K. E. (2002). Co-regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism. *Molecular pharmacology*, 62(1), 162–172. <https://doi.org/10.1124/mol.62.1.162>
36. Amirimani, B., Ning, B., Deitz, A. C., Weber, B. L., Kadlubar, F. F., & Rebbeck, T. R. (2003). Increased transcriptional activity of the CYP3A4*1B promoter variant. *Environmental and molecular mutagenesis*, 42(4), 299–305. <https://doi.org/10.1002/em.10199>
37. Shi, W. L., Tang, H. L., & Zhai, S. D. (2015). Effects of the CYP3A4*1B Genetic Polymorphism on the Pharmacokinetics of Tacrolimus in Adult Renal Transplant Recipients: A Meta-Analysis. *PloS one*, 10(6), e0127995. <https://doi.org/10.1371/journal.pone.0127995>
38. Concha, J., Sangüesa, E., Ribate, M. P., & García, C. B. (2024). CYP3A4*1B but Not CYP3A5*3 as Determinant of Long-Term Tacrolimus Dose Requirements in Spanish Solid Organ Transplant Patients. *International journal of molecular sciences*, 25(20), 11327. <https://doi.org/10.3390/ijms252011327>
39. Matsubara, Y., Kanazawa, T., Kojima, Y., Abe, Y., Kobayashi, K., Kanbe, H., Harada, H., Momose, Y., Terakado, S., Adachi, Y., & Midgley, I. (2006). *Yakugaku zasshi : Journal of the Pharmaceutical Society of Japan*, 126 Spec no., 237–245. <https://doi.org/10.1248/yakushi.126.237>
40. URL: https://ec.europa.eu/health/documents/community-register/2012/20120420122530/anx_122530_en.pdf
41. Hodges, L. M., Markova, S. M., Chinn, L. W., Gow, J. M., Kroetz, D. L., Klein, T. E., & Altman, R. B. (2011). Very important pharmacogene summary: ABCB1 (MDR1, P-glycoprotein). *Pharmacogenetics and genomics*, 21(3), 152–161. <https://doi.org/10.1097/FPC.0b013e3283385a1c>
42. Cross, B., Turner, R. M., Zhang, J. E., & Pirmohamed, M. (2024). Being precise with anticoagulation to reduce adverse drug reactions: are we there yet?. *The pharmacogenomics journal*, 24(2), 7. <https://doi.org/10.1038/s41397-024-00329-y>
43. Tian, Y., Lei, Y., Wang, Y., Lai, J., Wang, J., & Xia, F. (2023). Mechanism of multidrug resistance to chemotherapy mediated by P-glycoprotein (Review). *International journal of oncology*, 63(5), 119. <https://doi.org/10.3892/ijo.2023.5567>
44. Eken, E., Estores, D. S., Cicali, E. J., Wiisanen, K. K., & Johnson, J. A. (2023). A Pharmacogenetics-Based Approach to Managing Gastroesophageal Reflux Disease: Current Perspectives and Future Steps. *Pharmacogenomics and personalized medicine*, 16, 645–664. <https://doi.org/10.2147/PGPM.S371994>
45. Paré, G., Eriksson, N., Lehr, T., Connolly, S., Eikelboom, J., Ezekowitz, M. D., Axelsson, T., Haertter, S., Oldgren, J., Reilly, P., Siegbahn, A., Syvanen, A. C., Wadelius, C., Wadelius, M., Zimdahl-Gelling, H., Yusuf, S., & Wallentin, L. (2013). Genetic determinants of dabigatran plasma levels and their relation to bleeding. *Circulation*, 127(13), 1404–1412. <https://doi.org/10.1161/CIRCULATIONAHA.112.001233>
46. Lähtenmäki, J., Vuorinen, A. L., Pajula, J., Harno, K., Lehto, M., Niemi, M., & van Gils, M. (2021). Pharmacogenetics of Bleeding and Thromboembolic Events in Direct Oral Anticoagulant Users. *Clinical pharmacology and therapeutics*, 110(3), 768–776. <https://doi.org/10.1002/cpt.2316>

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