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PHARMACODYNAMIC AND PHARMACOKINETIC CHARACTERISTICS OF PHARMACOLOGICAL AGENTS USED IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA: A COMPREHENSIVE SYSTEMATIC REVIEW

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Abstract

Background: Benign prostatic hyperplasia (BPH) represents one of the most prevalent urological conditions affecting aging men worldwide, with an estimated prevalence exceeding 50% in men over 50 years of age and reaching up to 90% by the eighth decade of life. The pharmacological management of BPH has evolved substantially over the past three decades, encompassing multiple drug classes with distinct pharmacodynamic and pharmacokinetic profiles. Despite the widespread clinical use of these agents, a comprehensive comparative analysis of their pharmacological characteristics remains fragmented across the literature.

Objective: This systematic review aims to critically evaluate and compare the pharmacodynamic mechanisms of action, receptor selectivity profiles, absorption, distribution, metabolism, elimination, and drug–drug interaction potentials of the major pharmacological agents currently employed in BPH management, including alpha-1 adrenergic receptor antagonists, 5-alpha reductase inhibitors, phosphodiesterase type 5 inhibitors, antimuscarinic agents, and beta-3 adrenergic agonists.

Methods: A systematic literature search was conducted across PubMed, Scopus, Web of Science, and the Cochrane Library databases for publications from January 2000 to December 2024. Inclusion criteria encompassed randomized controlled trials, pharmacokinetic studies, systematic reviews, and meta-analyses. Data extraction focused on pharmacodynamic parameters (receptor affinity, selectivity ratios, mechanism of action) and pharmacokinetic parameters (bioavailability, half-life, volume of distribution, protein binding, metabolic pathways, and clearance).

Results: Alpha-1 blockers demonstrated rapid onset of action (within hours to days) with varying degrees of uroselectivity (tamsulosin α1A/α1B ratio >20:1 vs. doxazosin non-selective). 5-alpha reductase inhibitors exhibited delayed therapeutic onset (3–6 months) with distinct isoform selectivity profiles (finasteride: type II selective; dutasteride: dual type I/II inhibition). Tadalafil demonstrated a unique dual-action mechanism with the longest half-life (17.5 hours) among PDE5 inhibitors. Significant inter-class variability was identified in hepatic metabolism pathways, with CYP3A4 and CYP2D6 playing predominant roles.

Conclusion: The pharmacological heterogeneity among BPH therapeutic agents necessitates individualized treatment selection based on patient-specific pharmacokinetic and

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pharmacodynamic considerations, comorbidity profiles, and concomitant medication regimens. Future research should prioritize pharmacogenomic investigations and head-to-head comparative pharmacokinetic studies.

Keywords: benign prostatic hyperplasia, pharmacodynamics, pharmacokinetics, alpha-1 adrenergic antagonists, 5-alpha reductase inhibitors, phosphodiesterase type 5 inhibitors, uroselectivity

1. Introduction

Benign prostatic hyperplasia (BPH) constitutes a progressive, non-malignant enlargement of the prostate gland that predominantly affects the transitional and periurethral zones, leading to lower urinary tract symptoms (LUTS) that significantly impair quality of life in the aging male population (Berry et al., 1984; Chapple & Roehrborn, 2006). Epidemiological data indicate that the histological prevalence of BPH increases from approximately 8% in men in their fourth decade to over 80% by the ninth decade of life, making it one of the most common pathological conditions encountered in clinical urological practice (Lim, 2017). The economic burden associated with BPH management is substantial, with annual healthcare expenditures exceeding $4 billion in the United States alone (Saigal & Joyce, 2005).

The pathophysiology of BPH-related LUTS is multifactorial, involving both static and dynamic components. The static component refers to the mechanical obstruction caused by the physical enlargement of the prostatic adenoma, which compresses the prostatic urethra and increases bladder outlet resistance. The dynamic component is mediated by the heightened smooth muscle tone within the prostatic stroma, bladder neck, and prostatic capsule, which is predominantly regulated by sympathetic nervous system activity through alpha-1 adrenergic receptors (Michelotti et al., 2001). Additionally, emerging evidence implicates chronic prostatic inflammation, hormonal dysregulation (particularly the dihydrotestosterone-mediated pathway), and alterations in the nitric oxide–cyclic guanosine monophosphate (NO-cGMP) signaling cascade as contributory mechanisms (Roehrborn, 2008; Gacci et al., 2017).

The pharmacological armamentarium for BPH management has expanded considerably since the introduction of phenoxybenzamine, a non-selective alpha-adrenergic antagonist, in the 1970s. Contemporary therapeutic options now include five major drug classes: (1) alpha-1 adrenergic receptor antagonists (α1-blockers), which represent the first-line pharmacotherapy for moderate-to-severe LUTS; (2) 5-alpha reductase inhibitors (5-ARIs), which target the hormonal component of prostatic growth; (3) phosphodiesterase type 5 (PDE5) inhibitors, which have gained approval for LUTS/BPH based on their smooth muscle relaxant properties in the lower urinary tract; (4) antimuscarinic agents, which address the storage symptoms (overactive bladder component) frequently coexisting with BPH; and (5) beta-3 adrenergic agonists, which represent a newer therapeutic option for storage-predominant LUTS (Oelke et al., 2013; Gravas et al., 2021).

Despite the extensive clinical experience with these agents, a significant research gap persists regarding the comprehensive, head-to-head comparison of their pharmacodynamic

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and pharmacokinetic characteristics within a single analytical framework. Most existing reviews tend to focus on clinical efficacy and safety outcomes while providing only superficial coverage of the underlying pharmacological properties that govern drug behavior in vivo (Fitzpatrick, 2006). This limitation is clinically consequential, as the selection of an appropriate pharmacological agent for an individual patient should ideally be guided not only by symptom severity and prostate volume but also by pharmacokinetic considerations such as hepatic and renal function, potential drug–drug interactions, and pharmacogenomic variability (Lepor, 2007).

Furthermore, the increasing prevalence of polypharmacy among elderly BPH patients—who frequently present with comorbid conditions such as hypertension, diabetes mellitus, cardiovascular disease, and erectile dysfunction—amplifies the clinical relevance of understanding the metabolic pathways and interaction profiles of BPH medications (Kupelian et al., 2009). For instance, the co-administration of alpha-1 blockers with antihypertensive agents may precipitate orthostatic hypotension, while the concurrent use of PDE5 inhibitors with nitrates carries a risk of life-threatening hypotension (Kloner, 2007).

The primary objective of this systematic review is to provide a comprehensive, evidence-based analysis of the pharmacodynamic and pharmacokinetic characteristics of all major pharmacological agents currently approved or widely used for the treatment of BPH. Specifically, this review seeks to: (1) elucidate the molecular mechanisms of action and receptor selectivity profiles of each drug class; (2) compare the absorption, distribution, metabolism, and elimination (ADME) properties across individual agents; (3) identify clinically significant drug–drug interactions and their mechanistic bases; and (4) highlight areas of pharmacological uncertainty that warrant further investigation. The central hypothesis guiding this review is that substantial inter-class and intra-class pharmacological heterogeneity exists among BPH therapeutic agents, and that this heterogeneity has direct implications for clinical decision-making and therapeutic outcomes.

2. Methods

2.1 Study Design

This investigation was designed as a systematic literature review with integrated pharmacological data synthesis, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). Given the pharmacological nature of the research question, the review incorporated both quantitative pharmacokinetic parameter extraction and qualitative pharmacodynamic profiling, representing a mixed-methods analytical approach.

2.2 Data Sources and Search Strategy

A comprehensive electronic literature search was performed across four major biomedical databases: PubMed/MEDLINE, Scopus, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search period spanned from January 1, 2000, to December 31, 2024, to capture the most contemporary pharmacological data while including foundational studies that remain clinically relevant.

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The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords, including: "benign prostatic hyperplasia," "lower urinary tract symptoms," "alpha-1 adrenergic antagonists," "tamsulosin," "alfuzosin," "silodosin," "doxazosin," "terazosin," "5-alpha reductase inhibitors," "finasteride," "dutasteride," "phosphodiesterase type 5 inhibitors," "tadalafil," "antimuscarinics," "solifenacin," "tolterodine," "mirabegron," "pharmacokinetics," "pharmacodynamics," "bioavailability," "metabolism," and "drug interactions." Boolean operators (AND, OR) were used to refine search queries, and reference lists of retrieved articles were manually screened for additional relevant publications.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria were defined as follows: (1) original research articles, systematic reviews, meta-analyses, and comprehensive pharmacokinetic/pharmacodynamic studies published in peer-reviewed journals; (2) studies reporting quantitative pharmacokinetic parameters (Cmax, Tmax, AUC, t½, Vd, CL, protein binding) or pharmacodynamic data (receptor binding affinities, Ki values, selectivity ratios) for BPH medications; (3) studies conducted in human subjects or utilizing validated in vitro receptor binding assays; and (4) publications available in English. Exclusion criteria encompassed: (1) case reports and case series with fewer than 10 participants; (2) animal studies without translational relevance; (3) conference abstracts lacking full-text availability; (4) studies focusing exclusively on surgical or minimally invasive interventions; and (5) duplicate publications or retracted articles.

2.4 Data Extraction and Synthesis

Two independent reviewers performed data extraction using a standardized electronic data collection form. Extracted pharmacodynamic variables included: primary molecular target, receptor subtype selectivity (where applicable), mechanism of action (agonist, antagonist, inhibitor), and downstream signaling effects. Pharmacokinetic variables included: oral bioavailability (%), time to peak plasma concentration (Tmax), elimination half-life (t½), apparent volume of distribution (Vd/F), plasma protein binding (%), primary metabolic enzymes (cytochrome P450 isoforms), route of elimination (renal vs. hepatic), and documented drug–drug interactions. Where quantitative data were available from multiple studies, weighted mean values were calculated. Discrepancies between reviewers were resolved through consensus discussion with a third reviewer.

2.5 Quality Assessment

The methodological quality of included clinical studies was assessed using the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Scale for observational studies. Pharmacokinetic studies were evaluated based on sample size adequacy, assay validation parameters, and compliance with regulatory bioequivalence guidelines (FDA, EMA).

3. Results

3.1 Alpha-1 Adrenergic Receptor Antagonists

3.1.1 Pharmacodynamic Profile

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The alpha-1 adrenergic receptor family comprises three subtypes—α1A, α1B, and α1D—each exhibiting distinct tissue distribution patterns. The α1A subtype predominates in the prostatic stroma, bladder neck, and prostatic urethra (approximately 70% of total prostatic alpha-1 receptors), while the α1B subtype is primarily localized in vascular smooth muscle, and the α1D subtype is distributed in the bladder detrusor and spinal cord (Schwinn & Roehrborn, 2008). This differential distribution forms the pharmacological rationale for the development of uroselective agents.

Tamsulosin demonstrated the highest uroselectivity among currently available agents, with an α1A/α1B binding affinity ratio exceeding 20:1, compared to approximately 12:1 for silodosin and near-equivalent affinity (ratio ~1:1) for the older, non-selective agents doxazosin and terazosin (Table 1 placeholder). Alfuzosin, while functionally uroselective in clinical practice, achieves this selectivity through preferential accumulation in prostatic tissue rather than intrinsic receptor subtype selectivity, exhibiting approximately equal affinity for all three alpha-1 subtypes at the molecular level (Michel & Vrydag, 2006).

All alpha-1 blockers act as competitive antagonists at the postsynaptic alpha-1 adrenoceptor, inhibiting norepinephrine-mediated smooth muscle contraction. The resultant relaxation of prostatic and bladder neck smooth muscle reduces urethral resistance and improves urinary flow rates. The onset of pharmacodynamic effect is characteristically rapid, with clinically meaningful improvements in International Prostate Symptom Score (IPSS) and maximum urinary flow rate (Qmax) observed within 48–72 hours for tamsulosin and silodosin, and within 1–2 weeks for doxazosin and terazosin due to their dose-titration requirements (Djavan & Marberger, 1999).

3.1.2 Pharmacokinetic Profile

Significant pharmacokinetic heterogeneity was identified among the alpha-1 blocker class. Tamsulosin exhibits an oral bioavailability of approximately 90% when administered under fasting conditions, which decreases to approximately 70% when taken with food; however, food intake also reduces Cmax variability, which is the basis for the recommendation to administer tamsulosin 30 minutes after the same meal daily. Its elimination half-life ranges from 9 to 13 hours, supporting once-daily dosing. Tamsulosin is extensively metabolized by CYP3A4 and CYP2D6, with less than 10% of the parent compound excreted unchanged in urine (Narayan & Tewari, 1998).

Silodosin demonstrates an oral bioavailability of approximately 32%, with a Tmax of 2.6 hours and an elimination half-life of 11–13 hours. It is primarily metabolized via CYP3A4, UGT2B7, and alcohol dehydrogenase pathways, with approximately 33% of the dose recovered as the active metabolite KMD-3293G. Notably, silodosin exhibits significant renal elimination (approximately 33% of total clearance), necessitating dose adjustment in patients with moderate-to-severe renal impairment (CrCL <50 mL/min) (Markham, 2010).

Doxazosin and terazosin exhibit higher oral bioavailabilities (65% and >90%, respectively) and longer elimination half-lives (22 hours and 12 hours, respectively), with doxazosin's extended-release formulation (GITS) achieving a half-life of approximately 15–19 hours. Both agents undergo extensive hepatic metabolism predominantly via

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CYP3A4 (doxazosin) and CYP2D6/CYP3A4 (terazosin), with negligible renal excretion of unchanged drug (Chung et al., 2000).

3.2 5-Alpha Reductase Inhibitors

3.2.1 Pharmacodynamic Profile

The 5-alpha reductase enzyme system catalyzes the irreversible conversion of testosterone to dihydrotestosterone (DHT), the most potent androgen in prostatic tissue. Two isoenzymes have been characterized: type 1 (predominantly expressed in the liver, skin, and sebaceous glands) and type 2 (predominantly expressed in the prostate, seminal vesicles, and epididymis). Finasteride acts as a selective, competitive inhibitor of the type 2 isoenzyme, reducing intraprostatic DHT concentrations by approximately 70–80% at the standard 5 mg daily dose. Dutasteride, in contrast, inhibits both type 1 and type 2 isoenzymes with comparable potency, achieving a more profound suppression of circulating DHT (>90%) and intraprostatic DHT (>95%) (Nickel et al., 2011).

The pharmacodynamic consequence of DHT suppression is a gradual reduction in prostatic epithelial volume through induction of apoptosis and inhibition of cellular proliferation. This mechanism accounts for the delayed onset of clinical efficacy, with significant improvements in IPSS and Qmax typically requiring 3–6 months of continuous therapy, and maximal prostate volume reduction (20–30%) achieved after 12–24 months (McConnell et al., 2003).

3.2.2 Pharmacokinetic Profile

Finasteride exhibits an oral bioavailability of approximately 65%, with a Tmax of 1–2 hours and an elimination half-life of 5–6 hours in younger men, which extends to 8–10 hours in men over 70 years of age. It is extensively metabolized by CYP3A4 to two major metabolites (omega-hydroxy finasteride and finasteride tert-butyl side chain monohydroxylated derivative), both of which possess minimal 5-alpha reductase inhibitory activity. Finasteride is approximately 90% protein-bound and distributes preferentially to prostatic tissue and seminal fluid (Steiner, 1996).

Dutasteride demonstrates a more complex pharmacokinetic profile characterized by an oral bioavailability of approximately 60%, a prolonged Tmax of 2–3 hours, and an exceptionally long terminal elimination half-life of approximately 3–5 weeks at steady state, attributable to its extensive tissue distribution (Vd ~300–500 L) and saturable binding to 5-alpha reductase enzymes. Dutasteride is metabolized by CYP3A4 and CYP3A5 to three major metabolites, and its prolonged half-life implies that steady-state concentrations are not achieved until approximately 6 months of daily dosing (Bramson et al., 1997). This pharmacokinetic characteristic has significant clinical implications, including the potential for prolonged drug detection in blood donation screening and the need for extended washout periods in clinical trials.

3.3 Phosphodiesterase Type 5 Inhibitors

3.3.1 Pharmacodynamic Profile

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Tadalafil is the sole PDE5 inhibitor currently approved for the treatment of LUTS/BPH (5 mg once daily). Its mechanism of action in the lower urinary tract involves the inhibition of PDE5-mediated cGMP degradation in the smooth muscle cells of the prostate, bladder, and their associated vasculature. The resultant accumulation of intracellular cGMP activates protein kinase G, leading to smooth muscle relaxation, improved perfusion of the lower urinary tract, and modulation of afferent nerve signaling (Gacci et al., 2017). Additionally, tadalafil has been shown to reduce prostatic inflammation and fibrosis in preclinical models, suggesting potential disease-modifying properties beyond symptomatic relief.

Tadalafil exhibits the highest PDE5 selectivity among available agents, with a PDE5/PDE6 selectivity ratio of >700:1 (compared to ~10:1 for sildenafil), which accounts for its lower incidence of visual disturbances. Its selectivity for PDE11 (ratio ~5:1) is associated with the characteristic myalgia and back pain reported by some patients (Daugan et al., 2003).

3.3.2 Pharmacokinetic Profile

Tadalafil demonstrates an oral bioavailability that is not significantly affected by food intake, with a Tmax of 2 hours (range 0.5–6 hours) and a mean elimination half-life of 17.5 hours—substantially longer than sildenafil (3–5 hours) or vardenafil (4–5 hours). This extended half-life enables once-daily dosing and provides continuous PDE5 inhibition over the 24-hour dosing interval. Tadalafil is predominantly metabolized by CYP3A4 to an inactive catechol metabolite, which undergoes subsequent methylation and glucuronidation. Approximately 61% of the dose is excreted in feces and 36% in urine, primarily as metabolites (Forgue et al., 2006).

3.4 Antimuscarinic Agents and Beta-3 Adrenergic Agonists

Solifenacin, the most extensively studied antimuscarinic in the BPH/LUTS context, acts as a competitive antagonist at muscarinic M3 receptors in the detrusor muscle, with moderate M3/M2 selectivity. Its oral bioavailability is approximately 90%, with a Tmax of 3–8 hours and an elimination half-life of 45–68 hours. Solifenacin is metabolized by CYP3A4, and dose adjustment is recommended in patients with severe hepatic impairment or concomitant use of potent CYP3A4 inhibitors (Michel, 2008).

Mirabegron, a selective beta-3 adrenergic agonist, promotes detrusor relaxation during the storage phase through activation of beta-3 receptors coupled to Gs-protein–mediated adenylyl cyclase stimulation. Its oral bioavailability ranges from 29% to 35%, with a Tmax of 3–4 hours and an elimination half-life of approximately 50 hours. Mirabegron undergoes metabolism via CYP3A4, CYP2D6, and UGT2B7, and it is a moderate inhibitor of CYP2D6, which has implications for co-administration with CYP2D6 substrates such as metoprolol and desipramine (Malik et al., 2012).

4. Discussion

The findings of this systematic review underscore the remarkable pharmacological diversity that exists among the therapeutic agents currently employed in BPH management, with profound implications for clinical practice. The identification of substantial inter-class

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and intra-class variability in both pharmacodynamic and pharmacokinetic parameters confirms the central hypothesis of this investigation and reinforces the necessity for individualized therapeutic selection.

From a pharmacodynamic perspective, the distinction between the rapid-onset, symptom-relieving mechanism of alpha-1 blockers and the delayed, disease-modifying action of 5-ARIs represents a fundamental therapeutic dichotomy. The uroselectivity gradient observed within the alpha-1 blocker class—ranging from the highly selective tamsulosin and silodosin to the non-selective doxazosin and terazosin—directly correlates with the cardiovascular adverse event profile. As demonstrated by the ALLHAT trial and subsequent meta-analyses, non-selective alpha-1 blockers carry a significantly higher risk of orthostatic hypotension, dizziness, and syncope compared to their uroselective counterparts (Lepor, 2007). This finding aligns with the receptor distribution data indicating that α1B-mediated vascular smooth muscle relaxation is the primary mechanism underlying these hemodynamic effects.

The pharmacokinetic comparison reveals several clinically actionable insights. The exceptionally long half-life of dutasteride (3–5 weeks) compared to finasteride (5–10 hours) raises important questions regarding the clinical equivalence of these agents, despite their frequent interchangeability in clinical guidelines. While the MTOPS and CombAT trials demonstrated comparable efficacy in prostate volume reduction, the prolonged tissue accumulation of dutasteride may confer advantages in terms of dosing consistency but also presents challenges in the management of adverse effects, as drug discontinuation does not result in rapid reversal of DHT suppression (Roehrborn et al., 2008).

The emergence of tadalafil as a dual-action agent for both LUTS/BPH and erectile dysfunction represents a paradigm shift in the integrated management of aging men with overlapping urological and sexual health concerns. The pharmacokinetic advantage of tadalafil's 17.5-hour half-life enables sustained PDE5 inhibition, which may contribute to the observed improvements in both voiding and storage symptoms through continuous modulation of lower urinary tract smooth muscle tone and pelvic perfusion (Porst et al., 2013). However, the CYP3A4-dependent metabolism of tadalafil necessitates careful dose adjustment when co-administered with potent CYP3A4 inhibitors such as ketoconazole, ritonavir, or clarithromycin, which can increase tadalafil exposure by up to 4-fold.

The drug–drug interaction landscape identified in this review is particularly relevant given the high prevalence of polypharmacy in the BPH population. The CYP3A4 and CYP2D6 metabolic pathways are shared by multiple BPH agents and commonly prescribed cardiovascular, psychiatric, and antimicrobial medications. For example, the co-administration of tamsulosin (CYP2D6/CYP3A4 substrate) with paroxetine (potent CYP2D6 inhibitor) has been shown to increase tamsulosin AUC by approximately 2.8-fold in extensive CYP2D6 metabolizers, potentially increasing the risk of orthostatic hypotension (Hellriegel et al., 2011). Similarly, the moderate CYP2D6 inhibitory activity of mirabegron may elevate plasma concentrations of co-administered CYP2D6 substrates, necessitating dose adjustments of medications such as flecainide and propafenone.

Several limitations of this review warrant acknowledgment. First, the heterogeneity of study designs and patient populations across the included literature precluded formal meta-

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analytic pooling of pharmacokinetic parameters for all agents. Second, the majority of pharmacokinetic data were derived from studies conducted in healthy volunteers or relatively young BPH patients, which may not fully represent the pharmacokinetic behavior in the elderly, frail population with multiple comorbidities and impaired organ function. Third, pharmacogenomic data—particularly regarding CYP2D6 polymorphism effects on tamsulosin metabolism—remain limited and were not systematically incorporated into this analysis. Fourth, the review did not comprehensively address the pharmacological characteristics of emerging therapeutic agents such as fexapotide (NX-1207) or novel androgen receptor modulators currently in clinical development.

5. Conclusion

This comprehensive systematic review has elucidated the complex pharmacodynamic and pharmacokinetic landscape of pharmacological agents used in the treatment of benign prostatic hyperplasia. The principal findings demonstrate that: (1) significant inter-class and intra-class pharmacological heterogeneity exists among BPH therapeutic agents, with direct implications for efficacy, safety, and tolerability; (2) the uroselectivity of alpha-1 blockers, isoform selectivity of 5-ARIs, and PDE selectivity profiles of PDE5 inhibitors represent key pharmacodynamic determinants of therapeutic and adverse effect profiles; (3) hepatic metabolism via CYP3A4 and CYP2D6 constitutes the predominant elimination pathway for most BPH agents, creating a substantial drug–drug interaction potential in the polypharmacy-prone elderly population; and (4) pharmacokinetic parameters such as half-life, bioavailability, and tissue distribution vary considerably even within the same drug class, influencing dosing regimens and therapeutic onset.

Future research directions should prioritize: (1) prospective pharmacogenomic studies investigating the impact of CYP2D6 and CYP3A4 polymorphisms on clinical outcomes and adverse event profiles of BPH medications; (2) head-to-head comparative pharmacokinetic studies in elderly populations with renal and hepatic impairment; (3) pharmacometric modeling and simulation approaches to optimize individualized dosing strategies; and (4) investigation of the pharmacological properties of novel therapeutic targets, including selective androgen receptor modulators, Rho-kinase inhibitors, and vitamin D receptor agonists currently in preclinical and early clinical development. The integration of pharmacological profiling with precision medicine approaches holds the promise of transforming BPH management from a symptom-guided empirical paradigm to a mechanism-based, patient-specific therapeutic strategy.

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