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# Drug Adherence and Clinical Outcomes for Patients Under Pharmacological Therapy for Lower Urinary Tract Symptoms Related to Benign Prostatic Hyperplasia: Population-based Cohort Study

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**Abstract**

***Background:*** Little is known about drug adherence in men treated for lower urinary tract symptoms (LUTS). Benign prostatic hyperplasia (BPH) is one of the causes of LUTS.
***Objective:*** To examine adherence to pharmacological therapy and its clinical value in men with LUTS.
***Design, setting, and participants:*** Population-based cohort study using an administrative prescription database and hospital discharge codes for 1.5 million men aged ≥40 yr treated with alpha blockers (ABs) and 5-alpha reductase inhibitors (5ARIs) alone or in combination (CT).
***Interventions:*** Therapy with ABs and/or 5ARIs.
***Outcome measurements and statistical analysis:*** The 1-yr and long-term adherence; hospitalization rates for BPH and BPH surgery. Multivariate Cox proportional hazards regression model, propensity score matching, and sensitivity analyses.
***Results and limitations:*** The 1-yr adherence was 29% in patients exposed to at least 6-mo therapy. Patients on CT had a higher discontinuation rate in the first 2 yr compared to those on monotherapy ($p < 0.0001$). Overall hospitalization rates for BPH and BPH surgery were 9.04 and 12.6 per 1000 patient-years, respectively. A lower risk of hospitalization was observed for 5ARI compared to AB therapy (hazard ratio [HR] 0.46 and 0.23; $p < 0.0001$). CT was associated with a reduced risk of hospitalization for BPH surgery (HR 0.94; $p < 0.0001$) compared to AB. Discontinuation of drug treatment was an independent risk factor for hospitalization for BPH and BPH surgery (HR 1.65 and 2.80; $p < 0.0001$) regardless of therapeutic group. Limitations include the paucity of clinical measures and the absence of patient-reported outcomes.
***Conclusions:*** Adherence to pharmacological therapy for BPH is low and could affect clinical outcomes. Long-term 5ARI and CT use was associated with an independent reduced risk of hospitalization for BPH surgery. Our findings suggest the need for new strategies to increase patient adherence to prescribed treatment and more appropriate prescribing by physicians.
***Patient summary:*** Our research shows that adherence to prescribed pharmacological therapy is crucial in the management of patients suffering from lower urinary tract symptoms. Moreover, pharmacological therapy can prevent disease progression.


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## 1. Introduction

Benign prostatic enlargement (BPE) is common in older men and is caused by a histopathologic condition: benign prostatic hyperplasia (BPH). Clinical manifestations of BPH include symptoms, signs, and sequaele of bladder outlet obstruction caused by BPE [1]. The prevalence of moderate-to-severe lower urinary tract symptoms (LUTS) in the community is high, ranging from 22% among 50–59-yr-old men to 45% among those in their seventh decade. Only 19% of men suffering from LUTS due to BPE seek medical treatment and only 10.2% are pharmacologically treated [2–4].

The aim of pharmacological therapy for BPH is to improve the patient's quality of life by relieving urinary symptoms and preventing the development of complications. International guidelines suggest that patients with moderate-to-severe LUTS are best managed initially with drugs [5,6].

Five classes of drugs are available: phytotherapeutics, alpha blockers (ABs), 5-alpha reductase inhibitors (5ARIs), phosphodiesterase inhibitors, and antimuscarinics/beta3 agonists. Long-term combination therapy (CT) with ABs and 5ARIs is beneficial in terms of symptoms control and disease progression [7–9].

Although pharmacological treatment of BPH is a success story in urology, daily practice suggests that several medical needs remain unmet. Whether or not this is because of limited drug effects, inappropriate patient management, or low drug adherence remains unclear [4,10,11]. Drug regimens for LUTS related to BPH (LUTS/BPH) are particularly complex for several reasons (geographic, societal and cultural differences, medication costs, and local health policies).

There is little evidence available on the impact of long-term treatment and drug adherence on BPH progression in real life [12]. Data on adherence are of importance to understand possible unmet needs, to explore patient preferences, and to identify areas of intervention in health systems [13,14].

The aim of this study was to evaluate drug adherence and long-term clinical outcomes in patients under pharmacological therapy for LUTS/BPH.

## 2. Patients and methods

A population-based cohort study was conducted using record-linkage analysis of three databases: a drug prescriptions database, a civil registry, and hospital discharge records (HDRs) for 6.5 million subjects across 22 local Italian health authorities.

### 2.1. Data sources

All Italian citizens have equal access to health care services; hospital and pharmaceutical services are provided free or at a minimum charge as part of the National Health Service (NHS). The Italian national drug database includes information on prescriptions reimbursed by the NHS; drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification [15] and qualified with respect to dosage and date of the first and subsequent prescriptions from which adherence can be derived.

This cohort was linked to the HDR database, which includes information on primary diagnoses and up to five coexisting conditions, procedures performed, and dates for hospital admission and discharge. Diagnoses are classified according to the International Classification of Diseases-Ninth Revision, Clinical Modification (ICD9-CM) [16]. The Italian civil registry provides demographic information.

The study methodology adopted has been widely used to produce good epidemiology surveys [17,18]. The analysis was carried out in strict compliance with the national Italian regulations for full protection of the privacy rights of subjects included in the databases and in line with previous studies [17,18]. According to Italian law, no ethical approval is required for this type of analysis and no informed consent from patients was required.

### 2.2. Study design

The sample population consisted of men aged 40 yr or older who were prescribed medications for LUTS/BPH during the index period from January 1, 2004 to December 31, 2006. Only ABs and 5ARIs were considered in the analysis (ATC codes G04CA and G04CB, respectively). Other drugs were excluded because they are either not covered by the NHS or are not labeled for treatment of LUTS/BPH.

During the index period, the first prescription of a drug was considered the index date for patient inclusion. Drug adherence was measured only in patients receiving treatment for a minimum of 6 mo during the index period. Three different levels of exposure were evaluated: $\geq$6 mo, $\geq$10 mo, and $\geq$12 mo. Patients on treatment for more than 12 mo during the index period were followed up for 4 yr (median time). Patients who (1) stopped one of the three possible regimens (AB monotherapy, 5ARI monotherapy, or CT) for at least two consecutive months during the first year of treatment and at least 4 mo/yr during the follow-up period, or (2) switched regimen were considered as discontinued.

Patients were followed until BPH hospitalization or surgery or the last follow-up. Patients were excluded when they had a diagnosis of urethral stricture (ICD9-CM codes 598, 589.0, 598.00, 598.01, 598.1, 598.2, 598.8, and 598.9), prostate cancer (ICD9-CM codes 185, 198.82, 233.4, 236.5, 239.5, and V10.46), and/or a prescription for a gonadotropin-releasing hormone analogue and/or an antiandrogen agent in the 12 mo preceding the index day.

### 2.3. Clinical outcomes

The Charlson comorbidity index adapted to ICD9-CM was used as a surrogate measure of comorbidities [19]. Hospital admissions were recorded in patients receiving $\geq$1 yr of pharmacological therapy and were considered as BPH-related when hospital records included a primary diagnosis and/or surgical procedures related to BPH. The presence of an ICD9-CM 600.xx code as the primary diagnosis without surgical procedures was considered as BPH hospitalization. Because of the lack of clear and universally accepted indications for hospitalization for BPH, we included in the analyses all hospitalization events for hematuria, urinary infection, urinary retention, bladder stones, and obstructive acute renal failure related to BPH. ICD9-CM codes 57.0, 57.91, 57.92, 60.21, 60.29, 60.3, 60.4 for primary or secondary surgical procedures for any primary diagnoses were considered as hospitalization for BPH surgery. The occurrence of hematuria (ICD9-CM 599.7), bladder stones and diverticula (ICD9-CM 592.0, 592.1, 592.9, 594.1, 563.3), bladder neck obstruction (ICD9-CM 599.7), urinary retention and obstruction (ICD9-CM 788.20, 599.6), acute and chronic renal failure (ICD9-CM 584, 585, 586), hydronephrosis (ICD9-CM 591), and urinary infection (ICD9-CM 595.0, 595.4) was also assessed to capture and characterize severity factors.