



Trends in the pharmacological treatment of benign prostatic hyperplasia in the UK from 1998 to 2016: a population-based cohort study

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Abstract

Purpose To describe trends in the pharmacological treatment of BPH in the United Kingdom (UK) from 1998 to 2016.

Methods We created a cohort of men with a diagnosis of BPH between 1998 and 2016 using the Clinical Practice Research Datalink. Using Poisson regression, we estimated annual prescription rates of 5 α RIs, α -blockers, and combination therapy (5 α RIs + α -blockers). Adherence was defined by a proportion of days covered > 80%.

Results Our cohort included 192,640 men with BPH who generated 1,176,264 person-years (PYs) of follow-up. The mean age was 68.0 (standard deviation: 10.7) years. The prescription rate of all BPH medications during the study period was 347.6 per 100 PYs (95% CI 347.2–347.9). α -Blockers had the highest prescription rate (222.9 per 100 PYs, 95% CI 222.7–223.2); prescription rates of 5 α RIs and combination therapy were 69.1 per 100 PYs (95% CI 69.0–69.3) and 55.5 per 100 PYs (95% CI 55.4–55.7), respectively. The prescription rate for combination therapy was 19 times greater in 2013–2016 than in 1998–2000 (rate ratio: 19.2, 95% CI 18.6–19.7), while the prescription rates for 5 α RIs and α -blockers each doubled during this period (rate ratio: 1.86, 95% CI 1.84–1.88 and rate ratio: 2.02, 95% CI 2.01–2.04, respectively). The proportion of patients who were adherent at 1 year to 5 α RIs (32.3%), α -blockers (44.0%), and combination therapy (45.6%) was low.

Conclusion The prescription rate of BPH medications increased substantially between 1998 and 2016 in the UK, with the greatest relative increase observed with combination therapy. Adherence to BPH medications was low in this population-based study.

Keywords Five-alpha reductase inhibitors · Drug utilization · Pharmacoepidemiology · Benign prostatic hyperplasia · Alpha-blockers

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Background

Benign prostatic hyperplasia (BPH), also known as benign prostatic hypertrophy, is a condition affecting middle-aged and older men and is characterized by an enlarged prostate that restricts the normal flow of urine through the urethra

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[1]. It affects an estimated 15 million American men aged 30–79 years [2]. More than 50% of men aged 60–69 years have symptoms of BPH, with the prevalence increasing up to 90% in older age groups [1]. The prostate volume may increase over time in men with BPH with a subsequent worsening of lower urinary tract symptoms (LUTS), increased degree of bother, and acute urinary retention [3].

In the past 20 years, multiple treatment modalities for BPH have arisen, including watchful waiting, lifestyle changes, drug therapy, and surgical intervention [4]. Initial treatment typically consists of a strategy of watchful waiting and lifestyle modification [5]. For patients with symptomatic bother, BPH treatment progresses to medical therapy, including five-alpha reductase inhibitors (5 α RI) and α -adrenergic antagonists (commonly referred to as ‘ α -blockers’), and/or surgery [6]. α -Blockers relax the smooth muscle tone of the prostate and bladder neck, increasing urinary flow [7]. By reducing the prostate size by 20–30% within 3–6 months of use, [8] 5 α RI have been associated with a 50% reduction in total serum prostate-specific antigen level, [9] a 57% relative risk reduction for acute urinary retention, and a 48% relative risk reduction for surgery compared with placebo [10]. They have also been shown to improve quality of life [11].

With an aging population, an increasing prevalence of BPH, and the emergence of new pharmacological treatments for BPH (including combination therapy), there is a need to better understand the population-based treatment patterns for BPH. While a small number of previous studies had examined the patterns of BPH drugs, [12, 13] these studies did not provide a thorough assessment of the trends of the pharmacological treatment of BPH, describing the use of α -blockers only [13] or examining use over a short duration of follow-up only [12]. The objective of this study was therefore to describe the trends in the pharmacological treatment of BPH between 1998 and 2016 in the United Kingdom (UK).

Methods

Data source

We conducted a retrospective cohort study using data from the UK’s Clinical Practice Research Datalink (CPRD). CPRD data are documented by the trained general practitioners and contain the complete primary care medical records of more than 11 million patients from more than 700 general practices across the UK [14]. The CPRD includes over 40 years of longitudinal data and covers approximately 11% of the UK population, of which it is broadly considered to be representative with respect to age, sex, and ethnicity [14]. Participating practices record lifestyle information (BMI and smoking) and each episode of clinical events (symptoms,

diagnoses), preventive care, tests, immunizations, specialist referrals, hospital admissions and their major outcomes, and details related to death [14]. Clinical diagnoses are recorded using Read codes, a hierarchical clinical classification system containing over 96,000 codes [14]. The system also captures all prescriptions generated by the general practitioner using a drug product name and British National Formulary code, alongside the details regarding dosage and quantity [14]. Several validation studies have assessed the accuracy, completeness, and consistency of CPRD data and determined that these data are of high quality [14, 15].

This study underwent scientific and ethical review by the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (ISAC number 16_265A2, the protocol for which was made available to journal reviewers) and ethical review by the research ethics board of the Jewish General Hospital in Montreal, Canada.

Study population

We identified all patients with a Read code indicating the presence of BPH in the CPRD (Supplementary Table 1). This cohort consisted of all patients with BPH, and we refer to this cohort as the ‘prevalent’ cohort. This cohort served as the study population for our primary analysis. The date of cohort entry for this cohort was defined by the latest of: the date of BPH diagnosis, the date on which the patient turned 40 years of age, the date by which the patient had 1 year of observation time in the CPRD, or January 1, 1998 (the beginning of our study period). We also created a secondary cohort restricted to patients newly diagnosed with BPH during the study period. In this cohort, we excluded patients whose first BPH diagnosis occurred before January 1, 1998 or with less than 1 year of CPRD observation time. We refer to this cohort as the ‘incident’ cohort. The date of this first BPH diagnosis defined cohort entry in the incident cohort. From this cohort, we further excluded patients who received a prescription for a BPH drug in the year before this first diagnosis, those with a missing date for their first recorded BPH diagnosis, and men with a history of prostatism. From both cohorts, we excluded patients with a diagnosis of prostate cancer prior to cohort entry as 5 α RI and α -blockers can be used off-label for the treatment of prostate cancer or relieve symptoms associated with cancer treatment. In all analyses, patients were followed from cohort entry until a diagnosis of prostate cancer, departure from the CPRD, the end of the study period (March 31, 2016), or death, whichever occurred first.

BPH medications

The vast majority of medications used to manage the symptoms of BPH are α -blockers and 5 α RIs [16]. α -Blockers monotherapy are often considered the first-line pharmacotherapy for BPH [16]. The European Medical Agency (EMA) and the US Food and Drug Administration (FDA) have approved both selective (alfuzosin, silodosin, and tamsulosin) and non-selective (doxazosin, prazosin, and terazosin) α -blockers for the treatment of BPH. Non-selective α -blockers also inhibit α -adrenergic receptors found in the vascular smooth muscle and are also indicated for hypertension [5, 6, 17]. The two main 5 α RIs inhibitors approved in the UK for BPH treatment are dutasteride and finasteride [16]. Combination drugs are also available that include combinations of finasteride (5 α RI) and terazosin (α -blocker) or dutasteride (5 α RI) and tamsulosin (α -blocker). We defined combination therapy based on 1) the prescription of the two classes of drugs in a combined formulation as a single pill; or 2) the prescription of each class of treatment (5 α RIs and α -blocker) on the same date.

Statistical analyses

We first described patients' demographic and clinical characteristics at the time of cohort entry. These baseline characteristics included age in years, frequency of general practitioner visits in the prior year, prostate-specific antigen (PSA) level, lifestyle characteristics (body mass index [BMI], smoking), and Charlson Comorbidity Index (CCI). The rate of prescription was defined by the number of a prescription issued per 100 person-years of follow-up. Using Poisson regression, we estimated prescription rates and corresponding 95% confidence intervals (CIs) for 5 α RIs, α -blockers, and combination therapies between January 1, 1998 and March 31, 2016, overall and by time period. We estimated crude and age-adjusted rate ratios (RRs) and 95% CIs comparing each subsequent period to 1998–2000, with age modeled non-linearly using a restricted cubic spline with five knots. We performed all statistical analyses using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

We conducted four secondary analyses. First, we stratified our analyses by age. Second, we sub-classified prescriptions of 5 α RIs and α -blockers by molecule. Third, we repeated our analyses among patients with incident BPH. Finally, we estimated adherence to BPH therapies (5 α RIs, α -blockers, and combination therapy) at 1 and 2 years, with adherence defined by a proportion of days covered (PDC) of at least 80%. We assumed that prescriptions were for 30 days, and we included a 30-day grace period in our main adherence analysis. The PDC formula is described in detail in the Supplementary Methods. In addition, we assessed the

association between adherence and baseline patients' characteristics using multivariable logistic regression.

We conducted four sensitivity analyses to assess the robustness of our results. First, we assumed that prescriptions for a new class of drugs represented add-on therapy rather than a treatment switch. Second, we changed the reference category for our estimated RRs to the preceding period rather than using the 1998–2000 period. Third, we also estimated the rates and rate ratios for combination therapy sub-classified as either combination pills or two separate prescriptions issued on the same day. Finally, we repeated our adherence analyses without the inclusion of a grace period.

Results

Study population and patient characteristics

Among 231,174 patients with a diagnosis of BPH initially identified in CPRD, 192,640 patients met our inclusion criteria and were included in our primary cohort (Fig. 1). Table 1 presents the baseline characteristics of our BPH cohort. Overall, the mean age of BPH patients in the cohort was 68.0 ± 10.7 years. Patients prescribed 5 α RIs (72.8 ± 10.0 years) and combination therapy (72.1 ± 9.7 years) were older than patients with no prescription for BPH medication (67.2 ± 10.8 years) and those prescribed α -blockers (68.6 ± 10.2 years). Approximately,

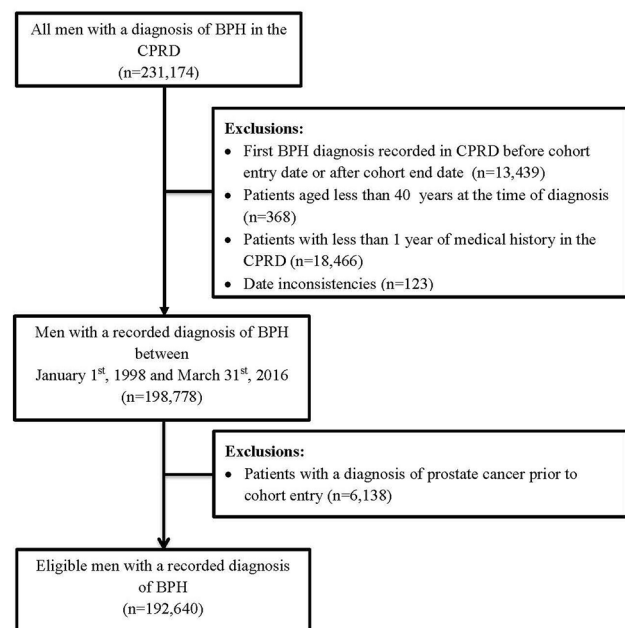


Fig. 1 Flow diagram describing the construction of the cohort of men with BPH in the UK between 1998 and 2016. *Benign prostatic hyperplasia, **Clinical Practice Research Datalink

Table 1 Baseline characteristics of primary cohort of men with BPH in the UK between 1998 and 2016

Patients characteristics	5 α RI (n = 8630)	α -Blockers (n = 50,864)	Combination treatment* (n = 7927)	No treatment (n = 125,219)	Total (n = 192,640)
Age, mean (SD)	72.8 (10.0)	68.6 (10.2)	72.0 (9.7)	67.2 (10.8)	68.0 (10.7)
< 55 years	356 (4.1)	4893 (9.6)	345 (4.4)	16,817 (13.4)	22,411 (11.6)
55–64 years	1544 (17.9)	13,750 (27.0)	1585 (20.0)	35,313 (28.2)	52,192 (27.1)
65–74 years	3020 (35.0)	17,989 (35.4)	2845 (35.9)	41,337 (33.0)	65,191 (33.8)
75–84 years	2736 (31.7)	11,693 (23.0)	2432 (30.7)	25,665 (20.5)	42,526 (22.1)
\geq 85 years	974 (11.3)	2539 (5.0)	720 (9.1)	6087 (4.9)	10,320 (5.4)
Calendar year, n (%)					
1998–2001	2148 (24.9)	8875 (17.5)	417 (5.3)	47,324 (37.8)	58,764 (30.5)
2002–2005	2162 (25.1)	12,254 (24.1)	1,170 (14.8)	29,601 (23.6)	45,187 (23.5)
2006–2009	2056 (23.8)	12,280 (24.1)	2125 (26.8)	23,542 (18.8)	40,003 (20.8)
2010–2013	1606 (18.6)	12,426 (24.4)	2836 (35.8)	17,779 (14.2)	34,647 (18.0)
2014–2016	658 (7.6)	5029 (9.9)	1379 (17.4)	6973 (5.6)	14,039 (7.3)
Lifestyle variables					
BMI, n (%)					
\geq 30 kg/m ²	1267 (14.7)	9646 (19.0)	1720 (21.7)	16,632 (13.3)	29,265 (15.2)
< 30 kg/m ²	4816 (55.8)	27,393 (53.9)	4555 (57.5)	63,889 (51.0)	100,653 (52.3)
Unknown	2547 (29.5)	13,825 (27.2)	1652 (20.8)	44,698 (35.7)	62,722 (32.6)
Smoking, n (%)					
Ever smoker	4436 (51.4)	28,040 (55.1)	4687 (59.1)	56,052 (44.8)	93,215 (48.4)
Never smoker	2537 (29.4)	14,257 (28.0)	2513 (31.7)	34,788 (27.8)	54,095 (28.1)
Unknown	1657 (19.2)	8567 (16.8)	727 (9.2)	34,379 (27.5)	45,330 (23.5)
PSA testing in the previous year, n (%)					
0–4 ng/ml	2092 (24.2)	15,190 (29.9)	2584 (32.6)	17,641 (14.1)	37,507 (19.5)
4–10 ng/ml	667 (7.7)	4223 (8.3)	900 (11.4)	6738 (5.4)	12,528 (6.5)
10–20 ng/ml	180 (2.1)	923 (1.8)	215 (2.7)	1907 (1.5)	3225 (1.7)
20+ ng/ml	69 (0.8)	413 (0.8)	73 (0.9)	1086 (0.9)	1641 (0.9)
Unknown	5622 (65.1)	30,115 (59.2)	4155 (52.4)	97,847 (78.1)	137,739 (71.5)
General practitioner visits, n (%)					
0	1.7 (3.6)	1.5 (3.3)	2.0 (4.0)	1.1 (2.9)	1.3 (3.1)
0	4735 (54.9)	29,072 (57.2)	4006 (50.5)	80,469 (64.3)	118,282 (61.4)
1–6	3324 (38.5)	19,046 (37.4)	3243 (40.9)	40,178 (32.1)	65,791 (34.2)
7–12	400 (4.6)	1984 (3.9)	492 (6.2)	3355 (2.7)	6231 (3.2)
13–24	137 (1.6)	628 (1.2)	151 (1.9)	997 (0.8)	1913 (1.0)
\geq 25	34 (0.4)	134 (0.3)	35 (0.4)	220 (0.2)	423 (0.2)
Charlson comorbidity index, n (%)					
0	3473 (40.2)	22,997 (45.2)	3018 (38.1)	65,292 (52.1)	94,780 (49.2)
1	2165 (25.1)	12,186 (24.0)	1738 (21.9)	30,059 (24.0)	46,148 (24.0)
2+	2992 (34.7)	15,681 (30.8)	3171 (40.0)	29,868 (23.9)	51,712 (26.8)

5 α RI five alpha reductase inhibitors; α -blocker alpha blocker; BPH Benign Prostatic Hyperplasia; CPRD Clinical Practice Research Datalink; n number; PSA prostate-specific antigen; SD standard deviation; UK United Kingdom

*Combination therapy included a 5 α RI inhibitor and an α -blocker

half of the patients had a BMI < 30 kg/m² (52.3%), and slightly less than half were recorded as ever smokers (48.4%). Patients with no BPH medication prescription and those prescribed α -blockers had fewer general practitioner visits and lower CCI scores than those prescribed 5 α RI or combination therapy.

Trends of BPH medications' prescriptions

Table 2 presents prescription rates and rate ratios for 5 α RI, α -blockers, and combination therapy overall and by calendar time. The median duration of follow-up was 1850 days (interquartile range 760–3422 days). Less than a third of

Table 2 Temporal trends in the prescription of BPH medications among men with BPH in the UK from 1998 to 2016

Prevalent Cohort (<i>n</i> = 192,640)						
Types of prescription	Years	No. of prescription	Person-years (PYs)	Prescription per 100 PYs	Crude rate ratios (95% CI)	Adjusted rate ratio (95% CI) ^a
α-Blockers only	1998–2000	111,969	90,861	123.2 (122.5–124.0)	1.00 (ref)	1.00 (ref)
	2001–2003	279,933	154,142	181.6 (180.9–182.3)	1.47 (1.46–1.48)	1.46 (1.45–1.47)
	2004–2006	447,361	209,460	213.6 (213.0–214.2)	1.73 (1.72–1.74)	1.70 (1.69–1.71)
	2007–2009	563,866	241,425	233.6 (233.0–234.2)	1.90 (1.88–1.91)	1.85 (1.83–1.86)
	2010–2012	625,615	251,131	249.1 (248.5–249.7)	2.02 (2.01–2.03)	1.96 (1.94–1.97)
	2013–2016	593,332	229,245	258.8 (258.2–259.5)	2.10 (2.09–2.11)	2.02 (2.01–2.04)
	1998–2016	2,622,076	1,176,264	222.9 (222.7–223.2)	–	–
5αRIs only	1998–2000	34,007	90,861	37.4 (37.0–37.8)	1.00 (ref)	1.00 (ref)
	2001–2003	67,791	154,142	44.0 (43.7–44.3)	1.18 (1.16–1.19)	1.11 (1.09–1.12)
	2004–2006	129,016	209,460	61.6 (61.3–61.9)	1.65 (1.63–1.67)	1.50 (1.48–1.52)
	2007–2009	183,944	241,425	76.2 (75.8–76.5)	2.04 (2.01–2.06)	1.79 (1.77–1.81)
	2010–2012	206,030	251,131	82.0 (81.7–82.4)	2.19 (2.17–2.22)	1.87 (1.85–1.89)
	2013–2016	192,288	229,245	83.9 (83.5–84.3)	2.24 (2.22–2.27)	1.86 (1.84–1.88)
	1998–2016	813,076	1,176,264	69.1 (69.0–69.3)	–	–
α-Blockers and 5αRIs combination therapy	1998–2000	4442	90,861	4.9 (4.8–5.0)	1.00 (ref)	1.00 (ref)
	2001–2003	15,771	154,142	10.2 (10.1–10.4)	2.09 (2.02–2.16)	2.01 (1.95–2.08)
	2004–2006	60,026	209,460	28.7 (28.4–28.9)	5.86 (5.69–6.04)	5.51 (5.34–5.68)
	2007–2009	128,545	241,425	53.2 (53.0–53.5)	10.89 (10.57–11.22)	9.98 (9.69–10.28)
	2010–2012	200,865	251,131	80.0 (79.6–80.3)	16.36 (15.88–16.85)	14.68 (14.25–15.13)
	2013–2016	243,548	229,245	106.2 (105.8–106.7)	21.73 (21.10–22.39)	19.16 (18.60–19.73)
	1998–2016	653,197	1,176,264	55.5 (55.4–55.7)	–	–
Overall prescription of BPH drugs	1998–2000	150,418	90,861	165.6 (164.7–166.4)	1.00 (ref)	1.00 (ref)
	2001–2003	363,495	154,142	235.8 (235.1–236.6)	1.42 (1.42–1.43)	1.39 (1.38–1.40)
	2004–2006	636,403	209,460	303.8 (303.1–304.6)	1.84 (1.83–1.85)	1.76 (1.75–1.77)
	2007–2009	876,355	241,425	363.0 (362.2–363.8)	2.19 (2.18–2.20)	2.07 (2.06–2.08)
	2010–2012	1,032,510	251,131	411.1 (410.4–411.9)	2.48 (2.47–2.50)	2.32 (2.31–2.33)
	2013–2016	1,029,168	229,245	448.9 (448.1–449.8)	2.71 (2.70–2.73)	2.50 (2.49–2.52)
	1998–2016	4,088,349	1,176,264	347.6 (347.2–347.9)	–	–

5αRI five alpha-reductase inhibitors; α-blocker alpha blocker; BPH Benign Prostatic Hyperplasia; CI Confidence Interval; *n* number; *ref* reference; UK United Kingdom

^aAdjusted for age using a restricted cubic spline

patients (27.3%) remained in the cohort until the end of the study period, while 21.8% of patients died during follow-up. The overall prescription rate of BPH medications over the study period was 347.6 per 100 PYs (95% CI 347.2–347.9). α-Blockers had the highest prescription rate (222.9 per 100 PYs, 95% CI 222.7–223.2), whereas 5αRIs and combination therapy had relatively lower prescription rates (69.1 per 100 PYs, 95% CI: 69.0–69.3 and 55.5 per 100 PYs, 95% CI: 55.4–55.7, respectively). The prescription of 5αRIs, α-blockers, and combination therapy steadily increased from 1998 to 2016 (Fig. 2, Table 2). The greatest relative increase occurred with combination therapy, with a prescription rate that was 19 times greater in 2013–2016 than in 1998–2000 (age-adjusted RR: 19.2, 95% CI 18.6–19.7). In contrast, the prescription rates for 5αRIs and α-blockers each doubled

during this period (age-adjusted RR: 1.86, 95% CI 1.84–1.88 and 2.02, 95% CI 2.01–2.04, respectively). Similar estimates were obtained when modeling age as a continuous variable, as a categorical variable, and non-linearly using a restricted cubic spline (Supplementary Table 2).

Secondary analyses

The rate of prescriptions not only increased over time, but also with age (Fig. 3). In particular, 5αRIs and combination therapy were prescribed 11 (RR: 11.4, 95% CI 11.2–11.6) and 9 (RR: 8.8, 95% CI 8.7–9.0) times more frequently in patients older than 85 years than in patients aged 40–54 years, respectively (Table 3, Supplementary Table 3, and Supplementary Fig. 1). In molecule-specific

Fig. 2 Prescription rates of BPH medications over time among men with BPH in the UK between 1998 and 2016

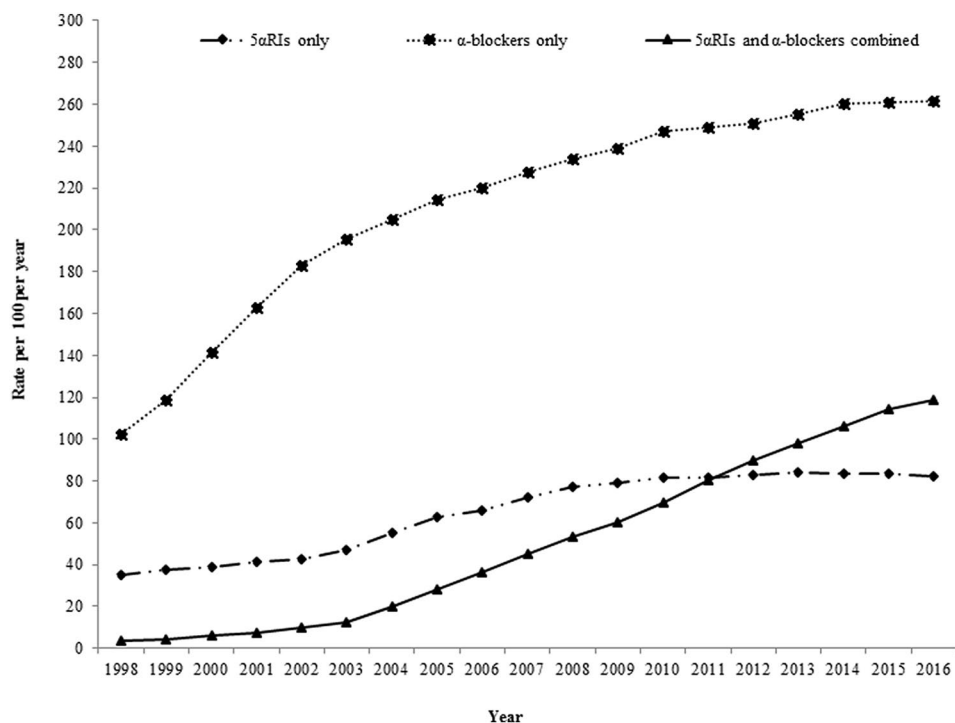
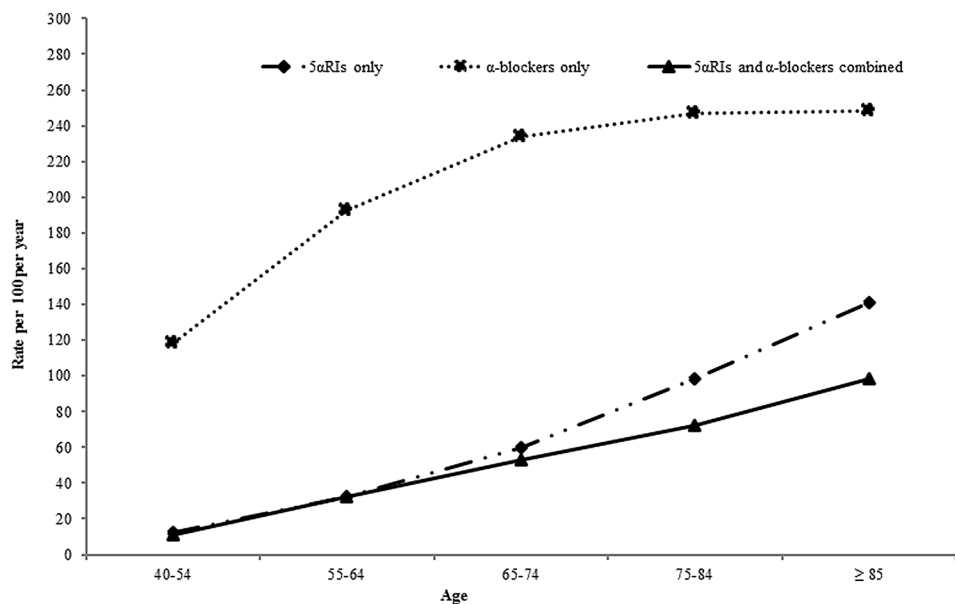


Fig. 3 Prescription rates of BPH medications by age among men with BPH in the UK between 1998 and 2016



analyses of 5αRIs drugs, similar trends were observed for both dutasteride and finasteride (Supplementary Table 4). In molecule-specific analyses of α-blockers, tamsulosin was most frequently prescribed and had the largest increase over time (Supplementary Table 5). The proportion of patients who were adherent at 1 year to 5αRIs (32.3%), α-blockers (44.0%), and combination therapy (45.6%) was low (Table 4). Baseline variables associated with adherence to 5αRIs were age, BMI, and CCI score

(Supplementary Table 6). Age, calendar year, BMI, smoking status, PSA testing, and CCI were associated with adherence to α-blockers. Age, calendar year, and PSA testing were associated with adherence to combination therapy. Finally, our analyses restricted to patients with incident BPH revealed similar trends as observed in the primary cohort (Supplementary Tables 7, 8 and 9 and Supplementary Figs. 2, 3, 4 and 5).

Table 3 Trends in the prescription of BPH medications among men with BPH in the UK from 1998 to 2016, by age at cohort

Prevalent cohort (*n* = 192,640)

Types of prescription	Age in years*	No. of prescriptions	Person-years	Prescription rate per 100 per year (95% CI)	Crude rate ratio (95% CI)
α-Blockers only	40–54	89,511	75,734	118.2 (117.4–119.0)	1.00 (ref)
	55–64	475,980	247,325	192.5 (191.9–193.0)	1.63 (1.62–1.64)
	65–74	963,384	411,298	234.2 (233.8–234.7)	1.98 (1.97–2.00)
	75–84	848,247	343,208	247.2 (246.6–247.7)	2.09 (2.08–2.11)
	≥ 85	244,954	98,699	248.9 (247.2–249.2)	2.10 (2.08–2.12)
	≥ 40	2,622,076	1,176,264	222.9 (222.7–223.2)	—
5αRIs only	40–54	9382	75,734	12.4 (12.1–12.6)	1.00 (ref)
	55–64	79,816	247,325	32.3 (32.1–32.5)	2.61 (2.55–2.66)
	65–74	247,231	411,298	60.1 (59.9–60.4)	4.85 (4.75–4.95)
	75–84	337,306	343,208	98.3 (98.0–98.6)	7.93 (7.77–8.10)
	≥ 85	139,341	98,699	141.2 (140.4–141.9)	11.40 (11.16–11.64)
	≥ 40	813,076	1,176,264	69.1 (69.0–69.3)	—
α-Blockers and 5αRIs combination therapy	40–54	8427	75,734	11.1 (10.9–11.4)	1.00 (ref)
	55–64	80,479	247,325	32.5 (32.3–32.8)	2.92 (2.86–2.99)
	65–74	218,505	411,298	53.1 (52.9–53.4)	4.77 (4.67–4.88)
	75–84	248,682	343,208	72.5 (72.2–72.7)	6.51 (6.37–6.65)
	≥ 85	97,104	98,699	98.4 (97.8–99.0)	8.84 (8.65–9.04)
	≥ 40	653,197	1,176,264	55.5 (55.4–55.7)	—
Overall prescription of BPH drugs	40–54	107,320	75,734	141.7 (140.9–142.6)	1.00 (ref)
	55–64	636,275	247,325	257.3 (256.6–257.9)	1.82 (1.80–1.83)
	65–74	1,429,120	411,298	347.5 (346.9–348.0)	2.45 (2.44–2.47)
	75–84	1,434,235	343,208	417.9 (417.2–418.6)	2.95 (2.93–2.97)
	≥ 85	481,399	98,699	487.7 (486.4–489.1)	3.44 (3.42–3.46)
	≥ 40	4,088,349	1,176,264	347.6 (347.2–347.9)	—

5αRI five alpha-reductase inhibitors; α-blocker alpha blocker; BPH benign prostatic hyperplasia; CI confidence interval; n number; ref reference; UK United Kingdom

*Age at cohort entry

Table 4 Adherence to BPH medications measured using the proportion of days covered in men with prevalent BPH in the UK between 1998 and 2016

Types of prescription	Grace period	Measurement window (years)	PDC		
			≥ 80%	Mean % (SD)	Median % (IQR)
5αRIs	30	1	32.3%	50.9 (36.5)	44.9 (15.3, 91.2)
	30	2	26.8%	44.2 (36.5)	31.7 (10.2, 84.0)
	0	1	27.8%	47.0 (34.3)	39.7 (15.1, 84.1)
	0	2	23.1%	40.7 (34.3)	28.4 (9.2, 76.3)
α-Blockers	30	1	44.0%	59.6 (37.2)	67.7 (18.9, 100.0)
	30	2	39.2%	53.9 (38.4)	54.9 (12.6, 95.2)
	0	1	38.7%	55.8 (35.1)	61.4 (16.4, 90.7)
	0	2	34.5%	50.4 (36.3)	49.9 (12.2, 88.2)
5αRIs and α-blockers combination therapy	30	1	45.6%	65.7 (32.7)	74.8 (35.9, 100.0)
	30	2	40.3%	59.6 (34.6)	65.9 (25.5, 94.3)
	0	1	39.6%	62.2 (31.1)	69.3 (33.3, 90.7)
	0	2	35.0%	56.4 (33.0)	61.1 (24.1, 88.0)

5αRI five alpha-reductase inhibitors; α-blocker alpha blocker; BPH benign prostatic hyperplasia; IQR interquartile range; PDC proportion of days covered; SD standard deviation; UK United Kingdom

Sensitivity analyses

Considering the prescription of a new class of drugs as add-on therapy rather than a treatment switch produced results that were consistent with those of our primary analysis. Changing the reference category to the preceding period attenuated the estimated RRs; all RRs remained greater than one except for the prescription of 5 α RIs during the 2013–2016 period, which showed a slight decrease compared to 2010–2012 (Supplementary Table 10). Finally, the sub-classification of combination therapy by formulation revealed that the observed increase in combination therapy occurred in individuals prescribed separate molecules on the same day, as combination pills only entered the market in 2010 and only accounted for a minority of combination therapy prescriptions by the end of the study period (Supplementary Table 11).

Discussion

The prescription rate of BPH medications in the UK considerably increased between 1998 and 2016. This increase was largely driven by the increased prescription of α -blockers, which accounted for 64% of all BPH medication prescriptions during the study period. The overall share of 5 α RI prescriptions was less than 20% and steadily increased from 1998 before stabilizing in 2010. Although the absolute rate of prescription was less than that of the monotherapies, the greatest relative increase was observed in the prescription rate combination therapy.

Trends in the prescription of α -blockers showed an increasing pattern largely driven by the prescription of tamsulosin between 1998 and 2016. This trend is consistent with the trends reported by previous studies [12, 13, 18]. After the FDA approval of the α -blocker tamsulosin in 1997, the prescription of α -blockers increased by twofold [19]. Several clinical guidelines such as those issued by the National Institute for Health and Care Excellence, [16] the European Association of Urology, [6] the American Urological Association, [20] and the Canadian Urological Association [21] recommend α -blockers as first-line therapy for men with moderate to severe LUTS and 5 α RIs to men with LUTS who have prostates estimated to be larger than 30 g. These recommendations emanate from the high clinical efficacy of α -blockers, their low adverse side effect profile, quick onset of action, and low costs [4].

The prescription rate of 5 α RIs also increased, doubling between 1998 and 2016. Despite this observed increase, the prescription rate for this class remains much lower than that of α -blockers. This lower prescription rate is consistent with the recommended use of 5 α RIs as second-line therapy [16]. It may also be due to their perceived safety profile; 5 α RIs are

associated with more serious adverse events than α -blockers, including erectile dysfunction and decreased libido [22]. The FDA has also issued a drug safety warning about increased prostate cancer risk with 5 α RIs in 2011, which may have affected physicians' and patients' treatment choices [2]. In addition, the uptake of dutasteride was slow in the UK, and general practitioners in the UK did not start prescribing it until 2003 [19].

The prescription rate for combination therapy substantially increased between 1998 and 2016. This trend might be due to the demonstration of the potential complementary mechanisms of these two classes of drugs [23]. In the 1990s, α -blockers were preferred over the combination therapy as a result of the Veterans Affairs Cooperative study [24] and the Prospective European Doxazosin and Combination Therapy Trial study, [25] which reported no difference in short-term effects between α -blocker monotherapy and combination therapy. In contrast, subsequent large randomized studies reported that long-term combination therapy could suppress the progression of BPH and reduce surgical interventions for BPH more effectively than either α -blocker or 5 α RIs monotherapies [26]. The rate of combination therapy increased fivefold after the publication of MTOPS study [19].

We found that adherence to BPH medications was low, with only 32.3, 39.2, and 45.6% of patients adherent at 1 year to 5 α RIs, α -blockers, and combination therapy, respectively. Adherence among BPH patients has been assessed previously; we reported higher adherence to BPH medication than previous studies [27, 28]. The difference in the study design and our use of PDC to define adherence represent the most likely reasons for this discrepancy. Most of the previous studies in this area defined adherence by discontinuation of therapy [27, 29] or using a medication adherence questionnaire [28]. However, a study by Nichol et.al, which used PDC as a measure of adherence, reported a comparable proportion of adherence (62% in combination therapy and 55% in α -blockers) as that reported here [29]. We also observed higher adherence with combination therapy than monotherapies. Patients with an advanced stage of BPH are more likely to be prescribed combination therapy, and the available literature suggests that patients with more severe disease and worse outcomes are less likely to complain about the side effects [30]. Ultimately, although the low levels of adherence may be attributable to potential side effects in routine clinical setting, [26, 29] future studies are needed to better understand the reasons behind these low levels of adherence.

This study has several strengths. First, the use of CPRD data allowed for a thorough analysis of population-based longitudinal trends of BPH medications prescriptions in the UK. These data are also well validated and have been the sources of over 2000 peer-reviewed publications [14]. Second, the CPRD records prescriptions written by the general

practitioner rather than pharmacy dispensing. Consequently, it provides a more valid measurement of treatment intentions. Third, we carried out several sensitivity analyses to assess the robustness of our results and repeated all analyses in the incident cohort.

This study also has potential limitations. First, the CPRD does not record prescriptions written by specialists; therefore, some misclassification is possible. However, BPH is a chronic condition that is typically managed in the primary care setting in the UK, where the general practitioner serves as the gatekeeper to the health-care system. Consequently, while the CPRD may not record some early prescriptions, most prescriptions for BPH medications will be issued by general practitioners and recorded in the CPRD. Second, we assumed that all prescriptions were for 30 days, as the most common prescription duration in the CPRD for medications used to treat chronic conditions is 28–30 days. Third, we defined combination therapy as either a prescription of a combination pill or prescription of both classes of medication on the same day, assuming that those who received prescriptions on different days switched treatments; sensitivity analyses that considered such prescriptions add-on therapy rather than switches produced results that were consistent with those of our primary analysis. Finally, we did not estimate the trends of other class of BPH medications prescriptions such as anti-muscarinic and phosphodiesterase inhibitors, as they were not commonly prescribed during the study period.

Conclusions

The overall rate of prescription of BPH medications substantially increased from 1998 to 2016 in the UK. This increase was largely driven by the increased prescription of α -blockers. The relative use of combination therapy also increased substantially over time, suggesting a trend toward a more aggressive approach to the pharmacological management of BPH. Low rates of adherence were observed for all classes of medication used to treat BPH.

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Author contributions HTA: contributed to the study design, defined the study variables' code, interpreted the results and drafted the

manuscript. PR: conducted the data management and analyses and critically reviewed the manuscript for important intellectual content. LA: critically reviewed the manuscript for important intellectual content. RWP: critically reviewed the manuscript for important intellectual content. JC: conducted the data management and analyses and critically reviewed the manuscript for important intellectual content. SB: critically reviewed the BPH codes definition and the manuscript for important intellectual content. KBF: developed the protocol, supervised the project, contributed to the interpretation of results, and critically reviewed the study variables' code and the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interest. The authors have nothing to disclose in particular relation to this study.

Research involving human participants and/or animals This study included men over the age of 40 years with the incident diagnosis of BPH. However, informed consent was not required (see below).

Informed consent Studies using the CPRD are not required to obtain informed consent from the individual study participants as data are anonymized. CPRD operates an opt-in model whereby a GP practice must provide consent for CPRD to collect de-identified primary care data from their practice. Patients at participating practices have the right to opt out of sharing and use of their data for research at any time and CPRD respects and abides by this choice.

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