

## 5-Alpha Reductase Inhibitors for Treatment of Benign Prostatic Hyperplasia: A Systematic Review and Meta-Analysis

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### Abstract

**Introduction:** Finasteride and dutasteride are competitive inhibitors of 5-alpha reductase (5AR) enzymes and are commonly used for the treatment of symptomatic benign prostatic hyperplasia (BPH). This study is intended to evaluate the literature regarding the relative efficacy of these two agents on clinically important outcomes.

**Method:** Randomized control trials, quasi-randomized trials, and systematic reviews comparing finasteride to dutasteride either as monotherapy or in combination with alpha-blockers in men with BPH were included. The outcomes studied included need for prostate-related surgery, acute urinary retention episodes, withdrawal due to adverse events, total serious adverse events, mortality, and sexual dysfunction.

**Results:** There were no differences in need for prostate-related surgery (OR 2.01, 95% CI: 0.18, 22.24), acute urinary retention episodes (OR 1.47, 95% CI: 0.68, 3.19), number of withdrawals due to adverse events (OR 1.10, 95% CI: 0.68, 1.75) or serious adverse events (1.31, 95% CI: 0.87, 1.97). The odds ratios for sexual dysfunction and total adverse events were 0.83 (95% CI: 0.64, 1.08) and 0.94 (95% CI: 0.78, 1.14) respectively.

**Conclusion:** There is insufficient evidence to suggest clinically important differences between finasteride and dutasteride at this time.

**Keywords:** Dutasteride; Finasteride; Prostatic hyperplasia; 5-alpha reductase inhibitors

### Introduction

5-alpha reductases (5AR) are the enzymes responsible for converting testosterone to dihydrotestosterone (DHT), which is important for the progression of benign prostatic hyperplasia (BPH). BPH is a common and progressive condition that could impair one's quality of life and affects men in an age-dependent manner; more than 50% of men over the age of 50 and close to 90% of men over 80 years old are affected [1]. It is characterized by various lower urinary tract symptoms, including decreased urinary stream, incomplete voiding, urinary frequency and hesitancy [2].

By blocking the enzyme, 5AR inhibitors decrease the serum concentration of DHT, inhibiting prostatic growth [3] and decreasing disease progression [2]. There are two 5AR inhibitors available: finasteride and dutasteride. Finasteride is a selective inhibitor of the Type 2 isoenzyme whereas dutasteride inhibits both Type 1 and Type 2 [4]. This difference in mechanism results in a significantly greater and more consistent reduction in DHT with dutasteride than finasteride [4,5]; however it is unclear whether this leads to a clinically significant difference.

There have been three systematic reviews on the use of dutasteride versus finasteride for the treatment of BPH [6-8] but these reviews contain several methodological issues that may affect the reliability of their findings. Bias may have been introduced through inclusion of retrospective cohort studies [7] and inadequate blinding around subjective symptoms [8]. One review only included results from one trial [7]. All previous systematic reviews limited their searches to English language only.

We felt the need to perform another systematic review and meta-analysis of RCTs to compare the efficacy and safety of finasteride and dutasteride in adult males with BPH, using a different methodological approach to address some of these issues.

### Methods

#### Research question and outcomes

We conducted this study to determine if dutasteride offers an advantage over finasteride in terms of the following clinically relevant outcomes:

- All-cause mortality
- Quality of life
- Serious adverse events
- Need for prostate-related surgery
- Acute urinary retention
- Improvement in symptoms
- Withdrawal due to adverse events
- Total adverse events
- Sexual dysfunction

#### Eligibility criteria

Studies were included if they were prospective randomized

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controlled trials, quasi-randomized controlled trials or systematic reviews; they compared finasteride and dutasteride head-to-head, either as monotherapy or in combination with alpha-blockers; they reported at least one clinically relevant outcome and the use of finasteride or dutasteride was not for alopecia or prevention or treatment of prostatic cancer. The targeted population was adult males with benign prostatic hyperplasia; no follow-up or language restrictions were specified.

### Study identification and selection

Articles were identified from Embase, Medline, PubMed, Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts, Cumulative Index to Nursing and Allied Health Literature and Latin American and Caribbean Literature on Health Sciences databases. These databases were searched from inception to July 2014. A combination of search terms were used including *prostatic hypertrophy, dutasteride, finasteride, quality of life, adverse drug reaction and mortality*. After removing duplicates and screening titles and abstracts, full texts of the chosen articles were obtained. All articles were screened and read independently by 2 reviewers. Reference lists of each included article were also reviewed for any additional studies. If any articles were missing information, the authors of the studies were contacted for clarification.

### Data extraction

Two authors independently collected data from included studies. Outcome values, including change in International Prostate Symptom Score (IPSS), need for surgery, acute urinary retention episodes, withdrawal due to adverse events, sexual dysfunction, serious adverse events and total adverse events were collected, if reported. Ethics approval was not required for this study.

### Quality assessment

We used the Cochrane risk of bias assessment tool to evaluate included studies [9]. Two reviewers independently rated the risk of bias and disagreements were resolved through consensus. We felt that the risk of bias assessment was more appropriate than a scoring system as it allows for transparency in how the bias was assessed from each study [9].

### Data analysis

For continuous outcomes, the mean difference from baseline to end of follow up with standard deviation (SD) was used as the summary statistic. For dichotomous outcomes, the odds ratio (OR) was used. When the absolute value for the mean difference was not provided, it was calculated from percent change from the baseline. When the SD of the change from baseline to the final measurement was not given, it was calculated using methods described in the Cochrane handbook [9].

To assess the heterogeneity between studies, the  $I^2$  statistic was used [9]. A funnel plot was planned to assess for publication bias if 10 or more trials were identified.

All data were analyzed using Review Manager 5.3 (Cochrane Collaboration, Copenhagen, DK).

## Results

See Figure 1 for specific details on the search. One trial did not have useable data [10] as the absolute number of participants was not provided. We contacted the author, but did not receive a response. A total of 1879 patients were included in the final analysis. Of the 4 included studies, one was blinded and three were open-label. Methods

of randomization were not specified in any of the studies. The process of allocation concealment was also not discussed. Study and patient characteristics can be found in Table 1; the results of the risk of bias assessment can be found in Figure 2. Two of the four studies used finasteride and dutasteride as monotherapies, while concurrent alpha-blockers were used in the others.

No studies reported mortality data although we it is very likely that all trialists have this data available. For this reason we rated all studies at high risk of bias in the “selective reporting” category. Change in quality of life results were too heterogeneous to be analyzed together. We chose to narratively summarize our findings. Three of the studies assessed quality of life using the IPSS score. One was able to demonstrate a statistically significant improvement with dutasteride compared to finasteride (10.4 point reduction compared to 6.3 in the Mohanty trial). In Jeong et al, the mean reduction for dutasteride was 5.8 points, whereas the reduction was 5.88 points in the finasteride group. In the study by Li et al, the reduction was 6.7 in the dutasteride group compared to 6 points in the finasteride group. In two of the three trials, blinding of participants and personnel was not performed [11,12] and was not mentioned in the third [13]. We were unable to identify the cause of heterogeneity between the three studies due to insufficient available information. It does not appear that improvement in quality of life differs for either agent.

Symptom improvement was reported by only one trial [14]. In this trial, dutasteride did not demonstrate a difference over finasteride (AUA-SI reduction of 5.8 points in dutasteride arm versus 5.5 points in finasteride arm). Although this trial was blinded to limit biases, it was not adequately powered to detect a difference.

Two studies reported on the need for prostate-related surgery; however, there were no events in one study, while the other did not report a statistically significant difference and was not adequately powered to detect a difference (see Figure 3).

The number of acute urinary retention episodes was reported in three studies, with two having no events. In the one study with events, no statistically different results were found although it was not powered to detect a difference (see Figure 4).

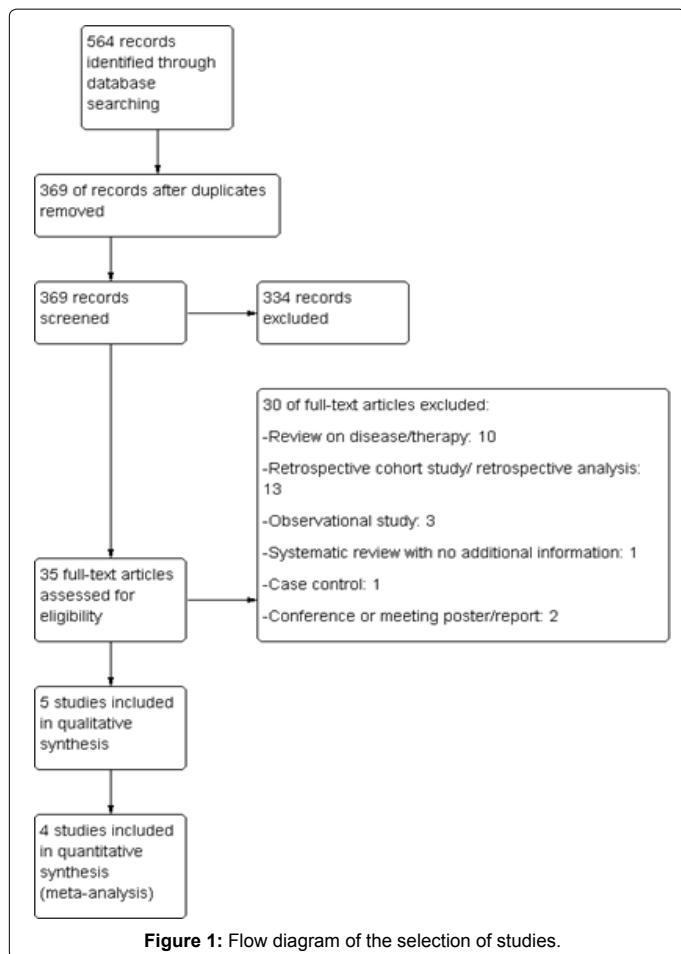
Of the three studies reporting on number of withdrawals due to adverse events, one study (Nickel) reported any events. In this trial, while there were numerically more withdrawals secondary to adverse events in the dutasteride group, this number was not statistically significant (see Figure 5). There were no statistically significant differences between dutasteride and finasteride in either number of patients experiencing serious adverse events (Figure 6) or total adverse events (Figure 7).

Our findings did not demonstrate a difference between dutasteride and finasteride with regards to sexual dysfunction (see Figure 8).

### Sensitivity analyses

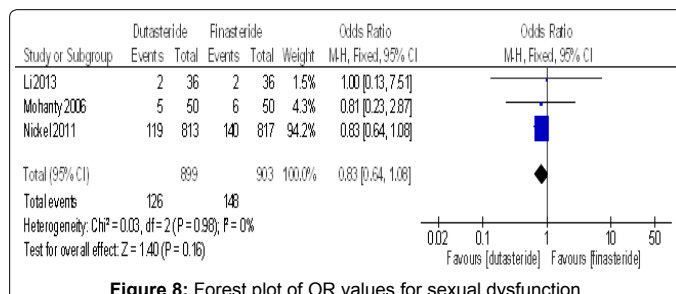
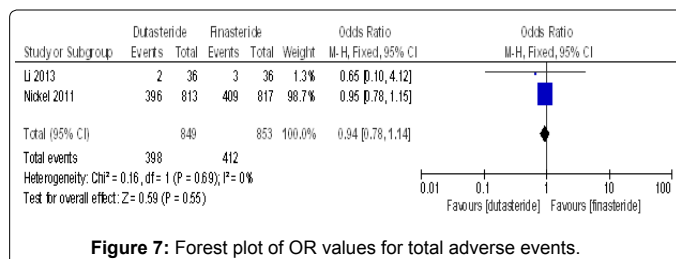
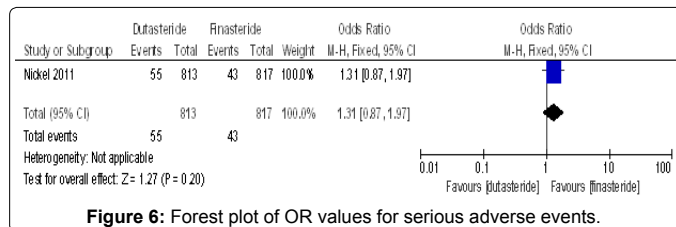
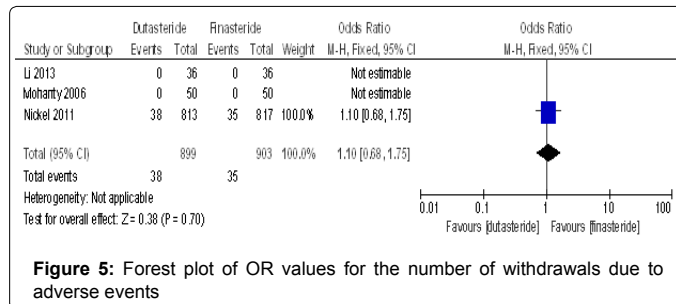
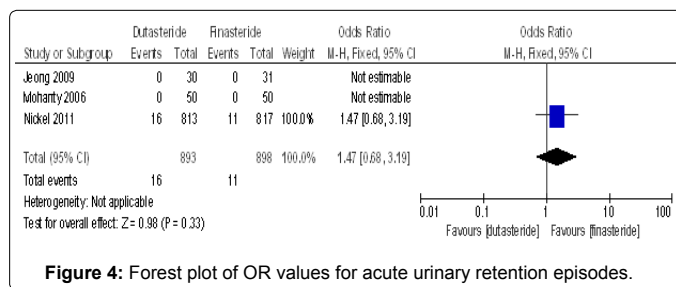
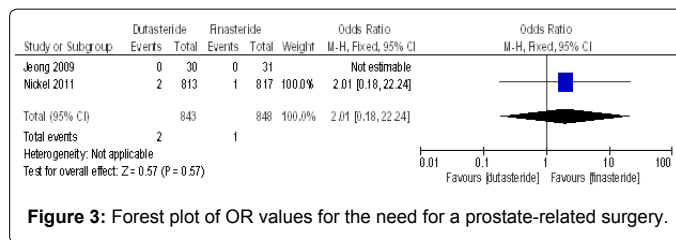
Removing trials that had at least one component rated as high risk of bias did not change the results of the analyses significantly. These trials had few patients, and in many analyses, had no events.

A sensitivity analysis was also conducted to assess the impact of patients who were lost to follow up. Numbers were adjusted in the various outcomes to assess worst-case scenarios where all patients lost to follow up in either arm experienced the outcome of interest. In these analyses, there was no change in the results.



|              | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|--------------|---|---|---|---|--|--------------------------------------|------------|
| Jeong 2009   | ?   | ?                                       | ?   | ?   | +  | -                                    | +          |
| Li 2013      | ?   | ?                                       | -   | -   | +  | -                                    | ?          |
| Mohanty 2006 | -   | -                                       | -   | -   | +  | -                                    | +          |
| Nickel 2011  | ?   | ?                                       | +   | +   | +  | -                                    | ?          |
| Ravish 2007  | ?   | ?                                       | +   | +   | -  | -                                    | -          |

**Figure 2: Risk of bias summary.**



| Study, Year   | Study Period | Number of participants | Main Inclusion Criteria   | Main Exclusion Criteria  | Treatment   | Control   |
|---------------|--------------|------------------------|---|--|---|---|
| Jeong, 2009   | 12 months    | 77                     | Men ≥ 50 years with moderate to severe BPH, on stable dose of uroselective alpha-blockers, prostate gland ≥ 25 cm <sup>3</sup>    | Chronic UTI, prostate/testicular surgery, prostate cancer, abnormal PSA, high probability of urinary obstruction likely to require surgery, AUR, chronically large postvoid residual urine volume, history of 5AR inhibitor  | Dutasteride 0.5 mg + alfuzosin 10 mg (or tamsulosin 0.2 mg) daily | Finasteride 5 mg + alfuzosin 10 mg (or tamsulosin 0.2 mg) daily |
| Li, 2013      | 6 months     | 72                     | Men with BPH, IPSS greater than 13, Qmax less than 15 mL/s, PSA less than 4 µg/L, urine volume less than 150 mL/urination         | Prostate cancer, urethra narrowing, bladder stone, urinary infections, neurogenic bladder, lower urinary track blockage/restriction, surgical interventions, BPH meds within 4 weeks prior to start of study, heart/lung/liver/kidney insufficiency  | Dutasteride 0.5 mg daily  | Finasteride 5 mg daily  |
| Mohanty, 2006 | 6 months     | 100                    | Men 40-80 years with BPH, no indication for surgery   | Suspected or diagnosed prostate cancer   | Dutasteride 0.5 mg + tamsulosin 0.4 mg daily at night             | Finasteride 5 mg + tamsulosin 0.4 mg daily at night             |
| Nickel, 2011  | 12 months    | 1630                   | Men ≥ 50 years with BPH, AUA-SI ≥ 12 points, prostate volume ≥ 30 cm <sup>3</sup> , Qmax <15 mL/s, minimum voided volume ≥ 125 mL | Post-void residual volume >250 mL, history or evidence of prostate cancer, previous prostatic surgery or invasive BPH treatment procedure, history of AUR in the past 3 months, PSA <1.5 ng/mL or 10 ng/mL, use of 5ARIs, use of alpha blockers within 2 weeks of screening visit and throughout study | Dutasteride 0.5 mg daily  | Finasteride 5 mg daily  |

UTI: Urinary Tract Infection; PSA: Prostate-Specific Antigen; AUR: Acute Urinary Retention; BPH: Benign Prostatic Hyperplasia; AUA-SI: American Urological Association - Symptom Index

**Table 1:** Characteristics of included studies.

## Discussion

We did not find any results to indicate that dutasteride or finasteride offers an advantage from a clinically relevant point of view. No statistically significant differences were detected in the outcomes examined from the identified studies.

Three systematic reviews have compared dutasteride and finasteride to date. Conte et al. found no head-to-head RCTs but drew conclusions from 3 retrospective cohort studies that dutasteride may be more effective in terms of acute urinary retention and need for surgery [6]. These findings are not consistent with our results, which did not demonstrate a statistically significant difference between the two agents. The contrast may be because our study included head-to-head RCTs and excluded retrospective studies to reduce bias. Observational, retrospective trials are at greater risk of confounding due to unknown baseline differences between groups [15]. Gacci et al. conducted another meta-analysis on treatments for BPH [7]. It reported findings from the only trial available, EPICS, which was also included in our review. Lastly, Park and Choi reviewed literature comparing dutasteride with placebo and finasteride. Although they were only able to compare dutasteride with finasteride for the outcomes of any adverse events or any drug-related adverse events, they found no difference between the two medications. Our review was able to identify an additional three trials by expanding the restrictions to include non-English and open-labelled trials. However, this additional data did not cause our findings to be substantially different [8]. Park and Choi did compare dutasteride to placebo and were successful in demonstrating that dutasteride produced a significant reduction in IPSS score compared to placebo. Our results may indicate that their findings may also be applicable to finasteride as there does not appear to be a demonstrable difference between the two agents.

Change in IPSS was an outcome that could not be meta-analyzed due to heterogeneity. It is also worth mentioning that three out of the four studies included were not blinded. As IPSS is a subjective measure in which patients evaluate their own symptoms, non-blinded studies carry high risk of bias; if patients know that they are on an experimental treatment, they may feel more positive about their symptom

improvement. A study done in 2012 concluded that effects reported by patients on subjective outcomes were considerably more optimistic in non-blinded studies than in blinded studies [16]. One unblinded trial showed a statistically significant improvement in quality of life for dutasteride compared to finasteride, but was the primary reason for heterogeneity in this outcome; excluding it from the analysis during sensitivity analysis eliminated all heterogeneity. Based on the available clinical trial evidence, both dutasteride and finasteride should produce similar improvements in BPH patients' quality of life.

The lack of statistical significance in our results could be due to an inadequate number of participants, which may represent a limitation of the present review. Of the 1879 patients included in this meta-analysis, 1630 were from the Nickel trial. This trial was powered to detect a change in prostate volume [4], but may be insufficiently powered to detect differences in other outcomes. Since the primary trial in the majority of analyses was not powered to detect differences in clinically important outcomes between the agents, it would be premature to declare that no difference exists between the two agents in these outcomes. In addition, blinded studies are required to assess the impact of clinically significant outcomes such as change in quality of life to be incorporated into future meta-analyses to determine whether true clinical differences exist between the two agents.

We only included RCTs with head-to-head comparisons of dutasteride and finasteride that reported clinically important health outcomes. Since it was our intent to apply research findings to real patient care in acute care settings, we felt the need to focus on clinical outcomes that matter to patients. For example, some commonly reported measures, such as prostate volume and urinary flow rate, are numbers that may not be meaningful to patients and their quality of life, and have not been correlated to patient quality of life [17,18]. We deemed them irrelevant for the purposes of this review. However, since some clinicians may disagree with our focus on clinically meaningful outcomes, it may limit the generalizability of this review to their practices.

We did not extend our search to grey literature, which may be a limitation of the present review. It is possible that additional results

could have been identified had we consulted regulators and conference proceedings.

We reviewed and included both English and non-English studies, which was not done in previous systematic reviews. Also, we used the Cochrane risk of bias assessment tool to evaluate the quality of our studies, which allows for more transparency in reporting than other bias scoring systems. Using the Cochrane risk of bias tool also eliminates the inherent weighting of biases that are incorporated in scoring tools [9].

## Conclusion

There is insufficient evidence to suggest clinically important differences between finasteride and dutasteride at this time.

## Acknowledgements

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