Cost analysis of fixed-dose combination of dutasteride and tamsulosin compared with concomitant dutasteride and tamsulosin monotherapy in patients with benign prostatic hyperplasia in Canada

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Abstract

Introduction: We estimate the lifetime cost of treatment for moderate/severe symptoms associated with benign prostatic hyperplasia (BPH) in a cohort of Canadian men aged 50 to 59, and we evaluate the costs of 2 daily bioequivalent treatment options: fixed-dose combination (FDC) of dutasteride (0.5 mg) and tamsulosin (0.4 mg), or concomitant administration of dutasteride (0.5 mg) and tamsulosin (0.4 mg) monotherapies.

Methods: The expected lifetime costs were estimated by modelling the incidence of acute urinary retention (AUR), BPH-related surgery and clinical progression over a patient's lifetime (up to 25 years). A model was developed to simulate clinical events over time, based on a discrete Markov process with 6 mutually exclusive health states and annual cycle length.

Results: The estimated lifetime budget cost for the cohort of 374 110 men aged 50 to 59 in Canada is between $6.35 billion and $7.60 billion, equivalent to between $16 979 and $20 315 per patient with moderate/severe symptoms associated with BPH. Costs are lower for FDC treatment, with the net difference in lifetime budget impact between the 2 treatment regimens at $1.25 billion. In this analysis, the true costs of BPH in Canada are underestimated for 2 main reasons: (1) to make the analysis tractable, it is restricted to a cohort aged 50 to 59, whereas BPH can affect all men; and (2) a closed cohort approach does not include the costs of new (incident) cases.

Conclusion: Canadian clinical guidelines recommend the use of the combination of tamsulosin and dutasteride for men with moderate/severe symptoms associated with BPH and enlarged prostate volume. This analysis, using a representational patient group, suggests that the FDC is a more cost-effective treatment option for BPH.

Introduction

Disease background

Benign prostatic hyperplasia (BPH) is a chronic condition which increases in incidence and prevalence with age.[1-3] An estimated 1.3 million men in Canada, 23% of the population of men 50 and over, experience moderate or severe symptoms of BPH.[4] BPH affects quality of life both directly, through lower urinary tract symptoms (LUTS), and indirectly, through anxiety about and fear of cancer. In patients who do not respond to medical treatments, or in cases of acute urinary retention (AUR), surgery may be necessary. The most common form of surgery, transurethral resection of the prostate (TURP), carries a risk of complications, including TUR syndrome, urinary incontinence and retrograde ejaculation.[5]

In a probability sample of 508 Canadian men 50 or older surveyed by telephone, 23% of respondents experienced moderate or severe symptoms associated with BPH.[4] The most prevalent symptoms were nocturia (62%), weak steam (61%) and urinary frequency (46%).[4] The Canadian Benign Prostatic Hyperplasia Audit Study (CanBas) carried out a prospective audit of urology outpatient practice. In total, 86 urologists were invited to participate, of whom 38 (44.2%) agreed. A total of 4324 men were seen by respondents during a 2-week audit period in April to June 2007; of these men, 849 were diagnosed with BPH (19.6% of men).[6]

Treatment options

The primary aim of treatment for BPH is to provide symptom relief and to prevent progression. Alpha-blockers and 5-alpha-reductase inhibitors (5-ARIs) constitute the 2 main pharmacological agents for the management of BPH/LUTS. Alpha-blockers (such as alfuzosin, doxazosin, tamsulosin,

terazosin and silodosin) work by relaxing smooth muscle in the prostate, bladder and blood vessels, increasing urinary flow rates and thereby improving symptoms. Alpha-blockers do not affect disease progression.[5] 5-ARIs (dutasteride, finasteride) block the conversion of testosterone to dihydrotestosterone, thus reducing cellular growth and in turn reducing the size of the prostate. In addition to providing symptom relief, 5-ARIs may also alter the natural history of BPH through a reduction in the risk of acute urinary retention (AUR) and the need for surgical intervention.[5]

Canadian guidelines for the diagnosis and treatment of BPH recommend alpha-blockers as a first-line option for men with bothersome symptoms. 5-ARIs, or a combination of an alpha-blocker and a 5-ARI, are recommended for patients with bothersome LUTS associated with prostatic enlargement.[5] The CanBas practice audit[6] confirmed that treatment patterns closely followed the Canadian guidelines. Medical therapy was the most common treatment, followed by transurethral resection of the prostate (TURP). The audit found that 51% of men were taking or had been prescribed an alpha-blocker, and 35% were on alpha-blocker monotherapy. Moreover, 25% of men were taking or had been prescribed 5-ARI therapy, either as monotherapy or as combination therapy. Combination therapy was used in 10% to 31% of men.

Study aims

Jalyn (GlaxoSmithKline) is a fixed-dose combination (FDC) of dutasteride 0.5 mg + tamsulosin 0.4 mg, available as an oral capsule in a daily single dose. There is evidence of bioequivalence between the FDC and concomitant dosing of dutasteride and tamsulosin.[7] The aims of the present study were to estimate the long-term costs of medical treatment for LUTS associated with BPH in patients with moderate to severe bothersome symptoms and enlarged prostates, and to compare costs with a FDC treatment versus costs with an oral, daily dutasteride (0.5 mg) and concomitant tamsulosin (0.4 mg) in Canada.

Methods

Analysis design

An analysis was carried out to estimate the lifetime costs of treating a cohort of patients with either (a) FDC therapy or (b) concomitant dosing with dutasteride and tamsulosin. We consider the costs falling on the public healthcare system in Canada, including the costs of medical treatment and dispensing fees, medical and surgical consultation, surgery and the costs of treating acute urinary retention (AUR). The time horizon is a patient lifetime (up to 25 years). Lifetime costs are assessed for a cohort representing the male population of Canada aged 50 to 59 years with diagnosed BPH and with moderate/severe lower urinary tract symptoms (LUTS), defined by prostate volume ≥30 cc and a score on the International Prostate Symptom Score (IPSS) ≥12, as per current Canadian treatment guidelines.[5] Based on a prevalence of moderate/severe symptoms of 15% in the relevant population in Canada,[4] the cohort for analysis is 374 111 men.

The aim of the analysis is to illustrate the costs of treatment for a representative sample of Canadian men, and for this reason the cohort selected for analysis (men aged 50-59) is less than the total population of men affected by the symptoms of BPH (typically men aged ≥50). The same principles apply to all men aged ≥50 years, but we have chosen a discrete subset simply to make the analysis more tractable (for example, to avoid the need to apply different prevalence rates according to age, and to avoid the complications implied in applying mortality rates to a population varying in age from 50 to 90+ years). The conclusions of the analysis are not affected by this simplification.

The analysis assumes no differences in outcomes between comparators, specifically in outcomes related to symptom relief and disease progression. This approach is justified by the results of an open-label, randomized, single-dose 3-period partial crossover study designed to test the bioequivalence and food effect of a FDC capsule formulation of dutasteride 0.5 mg and tamsulosin 0.4 mg, compared to concomitant dosing of dutasteride 0.5 mg and tamsulosin 0.4 mg.[7] The primary objective of the study was to investigate the bioequivalence of a combination capsule formulation relative to concomitant dosing in a fasted state and in a fed state.

In the fasted state, both the dutasteride and tamsulosin components of the FDC were bioequivalent to the reference formulations, assessed by comparison of bioavailability (AUC) and peak concentration (Cmax). The 90% confidence intervals for comparisons of AUC and Cmax were entirely contained within the interval 0.88 to 1.22.[7] Similarly, in the fed state, the 90% confidence intervals were in the range 0.92 to 116. Safety outcomes were similar between the FDC and reference formulations;[7] taken together, the evidence is consistent with the assumption of no significant difference in outcomes between the 2 comparators.

Model structure

Expected lifetime costs for the 2 comparators were estimated by modelling the incidence of AUR, BPH-related surgery and clinical progression over the patient's lifetime (in practice up to 25 years). A model was developed to simulate clinical events over time, based on a discrete Markov process with 6 mutually exclusive health states, including 1 temporary state (AUR), and annual cycle length. Health states were defined

as clinically meaningful and relevant in terms of their cost consequences. The 6 health states were: (1) mild BPH, (2) moderate BPH, (3) severe BPH, (4) AUR, (5) post-surgery, and (6) death. Mild, moderate and severe symptom states were defined by IPSS: 0-11 (mild), 12-23 (moderate) and 24-36 (severe), in line with the definitions used in the CombAT trial.[8] Details of the model structure are reported elsewhere.[9]

AUR was modelled as a temporary health state to reflect the fact that it is a short-term complication of BPH that requires emergency treatment. The patient pathway following AUR depends on the success of treatment (emergency catheterization or trial without catheter [TWOC]). Successful treatment leads to a return to the previous health state. Unsuccessful treatment requires BPH-related surgery, which leads to the post-surgery health state.

Although there are a number of surgical options for BPH, the model assumes all patients have had transurethral resection of the prostate (TURP) when surgery was indicated. Patients undergoing TURP enter the post-surgery health state, where they remain until the end of the model time horizon or death. A patient may undergo up to 2 TURP procedures (following failure of the first procedure or relapse). A patient may experience a surgery-related adverse event regardless of the success of the TURP procedure.

Patient cohort

The model cohort is males aged 50 to 59 years in Canada, diagnosed with BPH and with moderate/severe lower urinary tract symptoms, and reflects the CombAT trial population. In 2011 the male population of Canada in the relevant age group was 2.494 million.[10] Age-specific all-cause mortality rates for men were derived from Canadian national statistics[11] and were applied in the model.

Treatment efficacy

The model is driven by probabilities of events, such as AUR, BPH-related surgery, or death, and by assumptions about disease progression over time. These assumptions are reflected in annual probabilities of transition between health states. Most of the transitions populating the model were derived directly from the clinical study report or from individual patient-level data from the CombAT trial.[8]

Probabilities of transition from cycle 1 (year 1) were based on months 0 to 12 of the trial. Transition probabilities for remaining model cycles were based on months 13 to 48 of the trial. Patient-level information on health states was available at each 3 monthly study visits, and this information was used to derive probabilities for transitions between each of the symptom severity states.

Surgery and AUR transition probabilities were calculated using both the CombAT clinical study report and patient-level data. Three-month transition probabilities to the AUR and post-surgery health states were calculated from the number of yearly events using standard methods as described by Briggs and colleagues,[12] and transformed to annual probabilities for use in the model.

Rates of onward transition from AUR – either back to the previous BPH symptom state or to the post-surgery state – were determined by the success rate of a TWOC. The care pathway for patients experiencing AUR was not reported in the CombAT trial. For the model it was assumed that 50% of TWOC procedures are successful based on a clinical review by Emberton and colleagues[13] and input from Canadian clinicians. Similarly, the care pathway of patients who underwent BPH-related surgery was based on published literature.[14-16]

The costs of surgical and medical treatment–related adverse events were included in the analysis. The probability of any adverse event associated with TURP was determined from the European Association of Urology BPH treatment guidelines.[17] This total probability was applied to all patients in the post-surgery state, regardless of the success or failure of the procedure. Adverse events associated with medical therapy were based on the CombAT trial. Only those drug-related adverse events reported to have occurred in more than 1% of the population in any treatment arm were considered for inclusion in the model. Adverse events of a similar nature (such as retrograde ejaculation and ejaculation failure) were grouped together. The percentage of patients experiencing serious drug-related adverse events was <1% in all treatment arms of the CombAT trial, so serious drug-related adverse events were excluded from the analysis.

Resource use

Resource use included resources associated with disease severity states (maintenance healthcare visits or routine care), with AUR and with a TURP procedure. Since no newly diagnosed patients were considered in the analysis, the annual number of visits to health professionals varied with health state but not with time. Assumptions about the care of BPH patients in primary care and referral to secondary care and about treatment following AUR and BPH surgery were validated by Canadian clinicians.

Unit costs were derived from the Ontario Schedule of benefits,[18] the Quebec List of Medications[19] and resources detailed in a previous economic evaluation of combination therapy of doxazosin and finasteride in Canada (Table 1).[20] All costs are shown in 2011 Canadian dollars ($). Costs reported for a previous year were inflated to 2011 values using the consumer price index.[21] The analysis includes a dispensing fee of $10.50 per item.[18]

Table 1. Unit costs

Cost	Value	Source
Cost per district nurse visit	$45.15	Ontario Schedule of Benefits, 2012[18]
Cost per hospital nurse visit	$45.15	Ontario Schedule of Benefits, 2012[18]
Cost per GP visit	$77.20	Ontario Schedule of Benefits, 2012[18]
Cost per urologist visit	$80.00	Ontario Schedule of Benefits , 2012[18]
Cost per urodynamic test	$64.93	Inflated from McDonald, 2004,[20] using the Canadian pay and prices indices CADSIM 2011[21]
Cost per flexible cystoscopy	$71.00	Ontario Schedule of Benefits, 2012[18]
Cost of prostate-related surgery with complications	$4 249.44	Inflated from McDonald, 2004,[20] using the Canadian pay and prices indices CADSIM 2011[21]
Cost of prostate-related surgery without complications	$4 189.75	Inflated from McDonald, 2004,[20] using the Canadian pay and prices indices CADSIM 2011[21]
Cost per episode of AUR (non-elective)	$781.04	Inflated from McDonald, 2004,[20] using the Canadian pay and prices indices CADSIM 2011[21]
Monthly cost of fixed-dose combination (Jalyn, GlaxoSmithKline)	$48.82	Quebec List of Medications, 2012[19] Dosing information: Product monograph
Monthly cost of tamsulosin	$5.48	Quebec List of Medications, 2012[19] Dosing information: Product monograph
Monthly cost of dutasteride	$48.82	Quebec List of Medications, 2012[19] Dosing information: Product monograph
Dispensing fee	$10.50	Ontario Schedule of Benefits, 2012[18]

GP: general practitioner; AUR: acute urinary retention; month = 365/12 = 30.4167 days.

Results

Base case results

The total cost of treatment included the cost of medical treatment (tamsulosin and dutasteride or FDC combination therapy), dispensing fees, medical and surgical consultations, surgery, and AUR treatment. The lifetime estimated budget cost for the cohort of 374 110 men aged 50 to 59 in Canada in 2011 was between $6.35 billion and $7.60 billion, equivalent to between $16 979 and $20 315 per patient with moderate/severe symptoms associated with BPH (Table 2). The net present value of lifetime treatment costs, discounted at 5%,[22] is between $3.89 billion and $4.66 billion (Table 2).

Total treatment costs were accounted for primarily by the costs of medical treatment (56%-60% of the total) and dispensing fees (13%-22%) (Table 2). Other costs are consultations (12%-14%), surgery and AUR (11%-13%) (Fig. 1).

The estimated cost of medical treatment and dispensing fees depends on the choice of medical treatment regimen: fixed-dose combination (FDC) or concurrent tamsulosin plus dutasteride. The cost of FDC is lower than the concomitant therapy for 2 reasons: (1) because the price of FDC in Canada is the same as the price of dutasteride alone, the FDC price is lower by the price of tamsulosin ($5.48/month); and (2) because the FDC requires only one pharmacist dispensing fee rather than two, a saving of $10.50 per month. The net difference in lifetime budget impact between the 2 treatment regimens was $1.25 billion. The net present value of the difference in total treatment cost was $765 million (Table 2).

Sensitivity analysis

The sensitivity analysis considers a number of scenarios designed to reflect the cost impact of possible future changes in the characteristics of treatments. These analyses include a significant reduction in the cost of drugs, an assumption

Table 2. Total lifetime treatment costs (Canadian $ [billion])

	Undiscounted costs (budget costs)		Discounted costs (net present value)	
	Fixed-dose combination	Tamsulosin + dutasteride	Fixed-dose combination	Tamsulosin + dutasteride
Medical treatment	3.814 (60%)	4.242 (56%)	2.337 (60%)	2.600 (56%)
Dispensing fees	0.820 (13%)	1.640 (22%)	0.502 (13%)	1.005 (22%)
Consultations	0.896 (14%)	0.896 (12%)	0.549 (14%)	0.548 (12%)
Surgery and AUR	0.822 (13%)	0.822 (11%)	0.504 (13%)	0.504 (11%)
Total	6.352	7.600	3.892	4.657

AUR: acute urinary retention.

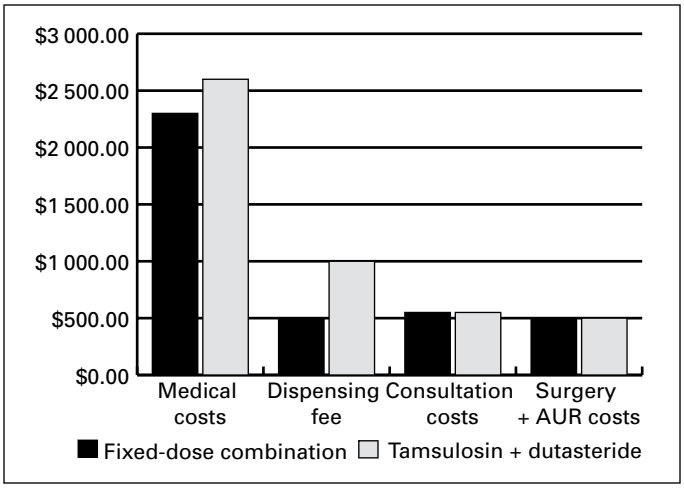

Fig. 1. Net present value of lifetime costs, by source of cost.

that prescriptions are written to cover 3-months' supply, rather than 1 month, and a reduction in the cost of surgical procedures that may be used instead of TURP (Table 3). At the present time tamsulosin is available as a generic, and dutasteride is available only in proprietary form. When a generic version of dutasteride becomes available, the cost of medical treatment may fall. In this scenario, the cost of a generic dutasteride is set equal to 25% of the current cost of the branded product ($12.21/month instead of $48.82). Total lifetime budget costs are reduced by $2.86 billion, from $7.6 billion to $4.74 billion. The net present value of costs is reduced by $1.7 billion, from $4.6 billion to $2.9 billion. The sensitivity analysis with a potential generic dutasteride and associated cost-savings may be considered representational of other generic 5-ARIs in the market.

In the base case, prescriptions are assumed to be written for a monthly course of treatment, and prescription fees are incurred every month. In this scenario, the prescription period is increased to 3 months, and this reduces the monthly prescription fee from $10.50 to $3.50. Total lifetime budget costs are reduced by between $546 million (FDC) and $1.094 billion (tamsulosin + dutasteride). The net present value of costs is reduced by between $336 million (FDC) and $671 million (tamsulosin + dutasteride).

TURP is the gold standard for patients who have failed conservative treatments,[5] but in recent years, other minimally invasive alternatives, such as transurethral vaporization of the prostate (TUVP) and transurethral microwave thermotherapy (TUMT), have been developed. In this scenario, the cost of TURP is reduced by 50% to investigate the impact of less-expensive future interventions. Total lifetime budget costs are reduced by $391 million, irrespective of the initial drug treatment, and the net present value of costs is reduced by $242 million.

Discussion

BPH is a chronic condition that affects more than 1 million men in Canada. Canadian treatment guidelines recommend alpha-blockers as a first-line treatment for men with bothersome symptoms. 5-ARIs are also recommended for patients with LUTS associated with enlargement of the prostate.[5] The CombAT trial[8] showed that the combination of dutasteride (0.5 mg) and tamsulosin (0.4 mg) significantly reduced the 4-year incidence of AUR, BPH-related surgery and overall clinical progression compared with either of the 2 monotherapies. Furthermore, combination therapy is recommended as an appropriate and effective strategy for patients with LUTS associated with prostate enlargement (>30 cc).[5]

A recent analysis has demonstrated the cost-effectiveness of oral, daily FDC of dutasteride (0.5 mg) and tamsulosin (0.4 mg) compared with oral, daily dutasteride (0.5 mg) or tamsulosin (0.4 mg) monotherapies from the perspective of the Canadian healthcare system.[9] Compared with tamsulosin, the FDC was more costly but also more effective. Over a patient lifetime, the incremental cost-effectiveness ratio (ICER) was $25 437 per quality-adjusted life year gained (QALY). At a willingness to pay $50 000 per QALY, the probability of the FDC being cost-effective was 99.6%. Compared with dutasteride, the FDC was a dominant option from year 2, offering better patient outcomes at a lower cost.[9]

The present study has evaluated the expected lifetime costs and relative cost-effectiveness of the FDC compared with concomitant tamsulosin and dutasteride in BPH patients who are candidates for combination therapy based on Canadian guidelines. Recent evidence has demonstrated the bioequivalence of the FDC and the 2 constituent monotherapies.[7] On this basis, cost-effectiveness is evaluated by comparing the net present value of lifetime costs of the 2 treatment options. The FDC is very likely to be the least

Table 3. Sensitivity analysis of total lifetime treatment costs (Canadian $ [billion])

	Undiscounted costs (budget costs)		Discounted costs (net present value)	
	Fixed-dose combination	Tamsulosin + dutasteride	Fixed-dose combination	Tamsulosin + dutasteride
Scenario 1: Generic dutasteride	6.352	4.740	3.892	2.904
Scenario 2: 3-monthly prescriptions	5.805	6.506	3.556	3.986
Scenario 3: 50% TURP cost	5.960	7.209	3.650	4.415

TURP: transurethral resection of the prostate.

costly and more cost-effective option in Canada. Lifetime costs for this cohort of Canadian men aged 50 to 59 with BPH in 2011 are expected to be lower by $1.25 billion, and the net present value of costs is expected to be lower by $765 million.

This study has a number of limitations. In particular, the analysis of a closed cohort consisting of a subgroup of the overall population with BPH provides only a partial estimate of the total cost of BPH in Canada. The analysis estimated lifetime treatment costs for a cohort of men aged 50 to 59 years with moderate to severe bothersome symptomatic BPH, as defined by current Canadian guidelines as suitable candidates for combination therapy. In practice BPH affects men of all ages, and in particular men over 50. In 2011, the Canadian population of men between 50 and 59 was 2.494 million, compared with 5.714 million aged over 50 years.[10] In a closed cohort model, cohort size decreases over time because of mortality. In practice, the population aged 50 to 59 years increases annually by the number of men reaching the age of 50. The net impact on the overall cohort size depends on the balance between mortality and new entrants. In addition, the closed cohort model is based on the prevalence of BPH in the starting population. In practice, the number of BPH cases increases annually because of new (incident) cases. The net effect depends on the incidence rate relative to the rate at which the condition is resolved (e.g., by surgery). These assumptions are necessary to make the model tractable. Estimates of the total lifetime treatment costs are likely to be underestimated, but the cost-effectiveness of FDC relative to concomitant tamsulosin and dutasteride will not be affected.

Conclusion

The combination of dutasteride and tamsulosin has been shown to significantly reduce the risk of AUR, BPH surgery and clinical progression compared to tamsulosin monotherapy. Current Canadian clinical guidelines recommend the 2 treatments together for patients with LUTS associated with prostate enlargement. This analysis has demonstrated that a FDC has a high probability of being less costly (and more cost-effective) than concomitant tamsulosin and dutasteride.

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Competing interests: Dr. Sayani and Dr. Ismaila are full-time employees at GSK and own stock in the company. Afisi Ismaila is also an assistant professor (part-time) in the Department of Clinical Epidemiology and Biostatistics at McMaster University, Hamilton, ON. Anna Walker and John Posnett are employees of Heron Evidence Development, which was funded by GSK to conduct an independent cost-effectiveness assessment of dutasteride-tamsulosin combination therapy. Dr. Bruno Laroche is a member of the Advisory Boards for Eli Lilly and Pfizer. He is also a speaker for GPs and urologists on behalf of Actavis, Astellas, GSK and Pfizer. Dr. Nickel has received payment for consultations for GSK, Taris Biomedical, Pfizer, Eli Lilly, Farr Labs, Astellas, Trillium Therapeutics and Ferring. He has also been a clinical trial investigator (within the past 2 years – includes investigator-initiated clinical research trials) for GSK, Taris Biomedical, Pfizer, Eli Lilly, Johnson and Johnson and Auxillium. He has been a paid speaker at international meetings for Astellas and Eli Lilly. Dr. Su was an employee of GSK at the time of this research. Dr. Su is currently a full-time employee at Sanofi and own stocks in the company.

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References

1. Trueman P, Hood SC, Nayak US, et al. Prevalence of lower urinary tract symptoms and self-reported diagnosed "benign prostatic hyperplasia," and their effect on quality of life in a community based survey of men in the UK. *BJU Int* 1999;49:410-5.
2. Verhamme KM, Dieleman JP, Bleumink GS, et al. Incidence and prevalence of lower urinary tract symptoms suggestive of benign prostatic hyperplasia in primary care: The Triumph project. *Eur Urol* 2002;42:323-8. http://dx.doi.org/10.1016/S0302-2838(02)00354-8
3. Garraway WM, McKelvie GB, Russell EBAW, et al. Impact of previously unrecognized benign prostatic hyperplasia on the daily activities of middle-aged and elderly men. *Br J Gen Pract* 1993;43:318-21.
4. Norman RW, Nickel JC, Fish D, et al. Prostate-related symptoms in Canadian men 50 years of age or older: Prevalence and relationships among symptoms. *Br J Urol* 1994;74:542-50. http://dx.doi.org/10.1111/j.1464-410X.1994.tb09181.x
5. Nickel JC, Mendez-Probst CE, Whelan TF, et al.; and the Canadian Prostate Health Council and the CUA Guidelines Committee. 2010 Update: Guidelines for the management of benign prostatic hyperplasia. *Can Urol Assoc J* 2010;4:310-6. http://dx.doi.org/10.5489/cuaj.10124
6. Nickel JC, Downey J, Benard F, et al. The Canadian Benign Prostatic Hyperplasia Audit Study (CanBas). *Can Urol Assoc J* 2008;2:367-73.
7. Cai G, Thiessen JJ, Baidoo CA, et al. Operating characteristics of a partial-block randomized crossover bioequivalence study for dutasteride, a drug with a long half-life: Investigation through simulation and comparison with final results. *J Clin Pharmacol* 2010;50:1142-50. http://dx.doi.org/10.1177/0091270009355155
8. Roehrborn CG, Siami P, Barkin J, et al.; and the CombAT Study Group. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur Urol* 2010;57:123-31. http://dx.doi.org/10.1016/j.eururo.2009.09.035
9. Ismaila A, Walker A, Sayani A, et al. Cost-effectiveness of dutasteride-tamsulosin combination therapy for the treatment of symptomatic benign prostatic hyperplasia: A Canadian model based on the CombAT trial. *Can Urol Assoc J* 2013;7:e393-401. http://dx.doi.org/10.5489/cuaj.12131. Epub 2012 November 14.
10. Statistics Canada. Estimates of population, by age group and sex for July 1, Canada, provinces and territories (Table 051-0001). http://www.statcan.gc.ca/pub/91-215-x/91-215-x2012000-eng.pdf. Accessed December 3, 2013.
11. Statistics Canada. Deaths and mortality rate, by selected grouped causes and sex, Canada, provinces and territories (Table 102-0552). http://www.statcan.gc.ca/pub/91-215-x/91-215-x2012000-eng.pdf. Accessed December 3, 2013.
12. Briggs A, Claxton K, Sculpher M. *Decision Modelling for Health Economic Evaluation.* Oxford University Press; 2006.
13. Emberton M, Anson K. Acute urinary retention in men: An age old problem. *BMJ* 1999;318:921-5. http://dx.doi.org/10.1136/bmj.318.7188.921
14. Harding C, Robson W, Drinnan M, et al. Predicting the outcome of prostatectomy using noninvasive bladder pressure and urine flow measurements. *Eur Urol* 2007;52:186-92. http://dx.doi.org/10.1016/j.eururo.2006.11.009
15. Semmens JB, Wisniewski ZS, Bass AJ, et al. Trends in repeat prostatectomy after surgery for benign prostate disease: Application of record linkage to healthcare outcomes. *BJU Int* 1999;84:972-5. http://dx.doi.org/10.1046/j.1464-410x.1999.00359.x
16. McConnell JD, Barry MJ, Bruskewitz RC, et al. Clinical Practice Guidelines, Number 8: Agency for Health Care Policy and Research. Rockville, MD: US Department of Health and Human Services; 1994. Benign prostatic hyperplasia: diagnosis and treatment. AHCPR publication no. 94-0582.
17. De la Rosette JJ, Alivizatos G, Madersbacher S, et al. EAU Guidelines on benign prostatic hyperplasia (BPH). *Eur Urol* 2001;40:256-63. http://dx.doi.org/10.1159/000049784
18. Ministry of Health and Long-Term Care: Ontario Schedule of Benefits. www.health.gov.on.ca. Accessed December 3, 2013.

19. Quebec List of Medications. www.ramq.gouv.qc.ca/en/regie/legal-publications/pages/list-medications.aspx. Acessed December 3, 2013.
20. McDonald H, Hux M, Brisson M, et al. An economic evaluation of doxazosin, finasteride and combination therapy in the treatment of benign prostatic hyperplasia. *Can J Urol* 2004;11:2327-40.
21. Statistics Canada. Consumer Price Index (CPI), 2009 basket (Table 326-0021). www5.statcan.gc.ca. Accessed December 3, 2013.
22. Canadian Agency for Drugs and Technologies in Health. Guidelines for the Economic Evaluation of Technologies. www.cadth.ca/media/pdf/186_EconomicGuidelines_e.pdf. Accessed December 3, 2013.

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