ORIGINAL RESEARCH

Testosterone therapy: Prescribing and monitoring patterns of practice in British Columbia

Jennifer A. Locke, MD*; Ryan Flannigan, MD*; Oliver P. Günther, MD; Sean Skeldon, MD; S. Larry Goldenberg, MD

Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada

*Co-first authors

Abstract

Introduction: Guidelines recommend that testosterone therapy (TTh) be restricted to men with a biochemical diagnosis of hypogonadism, and that therapeutic responses be titrated within the normal range.
Methods: Using four provincial longitudinal databases in British Columbia, we identified men prescribed TTh from 1997–2013. We characterized the prescribing and monitoring practices of TTh in the context of serum testosterone levels drawn prior to and following initiation of TTh in a population-based setting.
Results: In our analysis of 37 741 men who received at least one TTh prescription, 48% received injectable testosterone and the vast majority were treated by general practitioners. The number of prescriptions for men increased annually, particularly after 2008; 40% discontinued their treatment after their first or second prescription, while 27% received more than 10 repeats. The absolute percentage of pre- and post-serum testosterone levels ordered increased by 16% and 31% during the study period, respectively. However, after initiating TTh, only 36% of all the men had a followup serum testosterone level drawn. Of those with low serum testosterone levels prior to TTh, 49% remained biochemically hypogonadal following TTh, suggesting non-compliance or inadequate dosing.
Conclusions: Many men prescribed TTh did not continue beyond a short trial. While the practice of checking pre-and post-TTh testosterone levels improved over the study period, it is concerning that only one-third had a followup serum testosterone level and half remained biochemically low. Further education is required around TTh prescribing, dose titration, and monitoring to ensure both effective and safe prescribing practice.

Introduction

Testosterone therapy (TTh) is approved for the management of symptomatic hypogonadism. When compared to placebo, TTh is associated with improvements in quality of life, libido, depression, and erectile function, as confirmed by a recent systematic review and network meta-analysis of 87 randomized clinical trials and 51 non-randomized controlled studies.[1] Improved sexual functioning and quality of life compared to placebo was confirmed by a recent systematic review of 38 randomized clinical trials.[2] Rates of prescribing in the U.S. increased between three- and eight-fold from 2001–2014.[1,3,4]

Coinciding with the general increased rate of TTh prescriptions over recent decades, there has been a growing concern regarding inappropriate prescribing of testosterone and lack of adherence to guidelines in both the U.K. and U.S.[4] Multiple international guidelines recommend that symptomatic men may benefit from TTh only if their symptoms were associated with biochemical confirmation of hypogonadism (i.e., a total testosterone level ≤300 ng/dL (<10.4 nmol/L) on two or more morning samples[5-8]). Despite congruent international guidelines on this, an increasing number of men may be receiving TTh despite being eugonadal, or even without any pre-TTh testing for a biochemical diagnosis, thus, without medical indication.[4] We sought to explore adherence to prescribing and monitoring practices as outlined by international guidelines in a Canadian healthcare environment that does not have the same fiscal pressures as are present in other privatized healthcare environments. We accessed, linked, and analyzed four longitudinal provincial databases to address these pertinent issues.

Methods

We interrogated the population-based administrative health datasets of British Columbia (BC), Canada for the years 1997–2013, under the regulatory approval of UBC Clinical Research Ethics Board (certificate H14-01366). BC has a universal healthcare system for its 4.7 million (as of 2015) residents.[9] The following databases were available: 1) Discharge Abstracts Database (DAD), containing hospitalization information, including admission date and up to 25 discharge diagnoses coded using International Classification of Diseases, 9th (ICD-9) or 10th (ICD-10) revisions;[10] 2) Medical Services Plan (MSP), which contains all outpatient service dates, diagnoses,

and procedural codes;[11] 3) PharmaNET, which contains dispensing information, such as unique drug identifiers, service date, dispensed quantities and days of supply, and medication;[12] and 4) outpatient laboratory results.

The PharmaNET data was used to identify men with a first testosterone prescription during the study period, and to extract their age and respective prescriber type. A set of exclusion criteria were applied based on ICD, hospital, and MSP codes to exclude men with prostate cancer, Klinefelter syndrome, testicular tumors, or pituitary abnormalities. A wash-in and wash-out period of one year allowed identification of pre- and post-treatment tests within 365 days of TTh. This period also addressed the potential problem of a man being included in the first year (1997) of our analysis as a first time TTh when, in fact, it might be a repeat TTh for him.

Labvision and Sunquest datasets were combined with the LifeLabs data and when multiple rows were found in the combined testosterone lab datasets with the same lab test descriptor, collection date, test value, unit, and reference range, only one of the rows was kept. Distribution of test labels and same-day co-occurring tests were tabulated and used to check for consistency.

To address the challenge of possible missing tests in the lab test datasets, the MSP data was used to identify testosterone tests based on billing codes 92266 (total testosterone) and 92265 (until 2011), and 92267 (2011 onwards). Similar to the lab test data, the distribution of MSP billing codes and same-day co-occurrences were tabulated and used to check for consistency. The MSP data was used to determine how many pre- and post-treatment testosterone tests were performed and, thus, to estimate the proportion of missing results in the lab test data from Population Data BC. For the analysis, it was assumed that relative proportions of lab test result categories were representative of the proportions that would be observed in the complete dataset if it were available.

The cumulative rate of pre- or post-treatment testosterone tests was determined by dividing the number of men with a pre- or post-treatment test by the overall number of men with first TTh. A one-year time interval was used to relate tests to TTh and rates were determined over the period 1998–2013 for pre- and 1997–2012 for post-treatment tests.

PharmaNET data was used to determine prescription types (drug formulation) for first TTh. Number of first TTh, prescriber type, prescription type, and total testosterone lab test value categories (when available) were aggregated by year, and corresponding counts or percentages were plotted to display trends and patterns over time. Histogram displays were created to illustrate the age distribution at first TTh and for the difference in number of days of closest testosterone tests pre- and post-treatment.

Trend analyses were performed with linear regression. Residual plots and 95% confidence intervals (CI) were checked before significance of a trend was reported.

Results

The data provided by Population Data BC identified 40 878 men who received TTh in BC between January 1, 1997 and December 31, 2013; after exclusion criteria were applied, 37 741 men represented the TTh cohort studied in subsequent analyses.

Characteristics of patients receiving first TTh prescription

A total of 14 889 (39.5%) of the men received only one (26%) or two (13.5%) prescriptions, suggesting a short trial of therapy with subsequent discontinuation of drug; 3217 men (8.5%) received three, 9460 (25.0%) men received 4–10, and 10 175 (27.0%) men received more than 10 testosterone prescriptions over the 17-year period.

There was a 1.57-fold increase in prescriptions overall from 1998–2013, with a transient increase between 2001 and 2004, and a rising trend from 2008 onwards in men under age 80 (Fig. 1A). In terms of percentage change for each of the age groups over the study period, age groups 51–60 and 71–80 showed small but significant trends, with percentage changes of 0.38% (95% CI 0.16, 0.60) and -0.28% (95% CI -0.35,-0.21) per year, respectively. Age
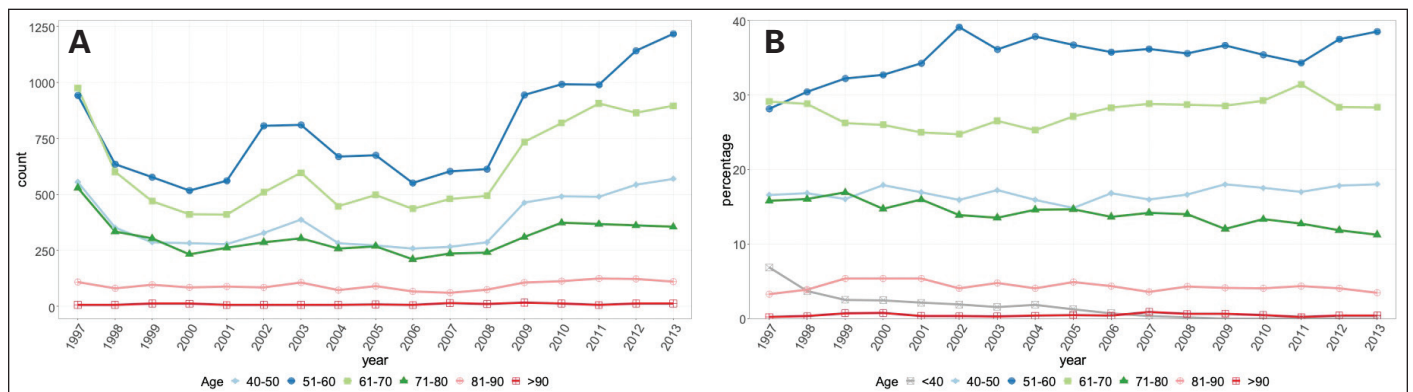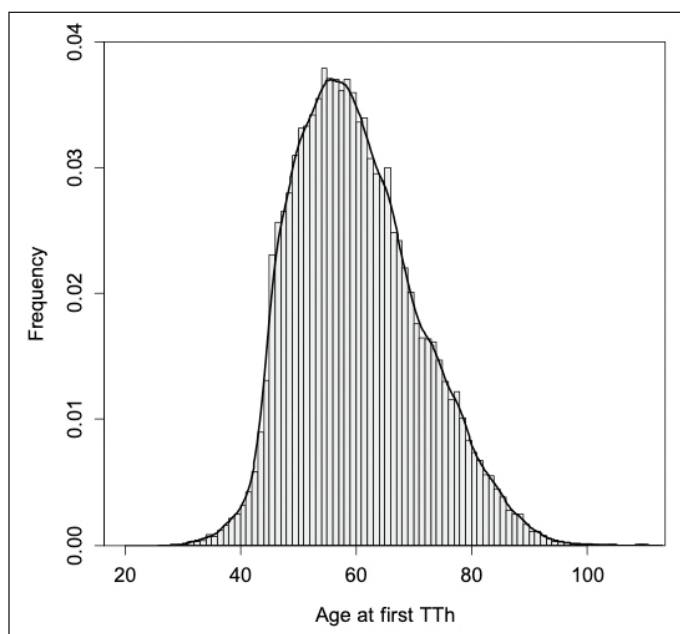

Fig. 1. Annual distribution of **(A)** first testosterone therapy prescription counts and **(B)** percentage for 37 741 men from 1997–2013, stratified by age at first treatment. *576 men younger than 40 years of age at time of first treatment were excluded in **Fig. 1A.**

group 61–70 had a percentage increase of 0.17% (95% CI 0.02, 0.33) per year, while age groups 40–50, 81–90 and >90 displayed small, non-significant changes (Fig. 1B). The youngest and oldest ages at first TTh prescription were 28 and 109 years old, and the mean and median ages at first TTh were 60 and 59 years (Fig. 1C). Standard deviation and median absolute deviation were 11 years.

TTh prescription types

Overall, most prescription types were injectables (48%), followed by oral capsules (25%), gels (24%), and patches (3%) (Fig. 2). Prior to 2001, only two treatments were available: injectables and capsules. From 1998–2000, there was a significant decrease in injectables, -3.36% per year (95% CI -3.88, -2.83), and a significant increase in capsules, 3.36% per year (95% CI 2.83, 3.88). From 2001–2004, with the introduction of other formulations, both the injectable and capsule prescriptions decreased as the newer formulations increased. The proportionate use of gel prescriptions increased steadily from 2005 (26%) to 2013 (43%), with an annual increase of 2.29% (95% CI 1.83, 2.76). During these years, linear downward trends were found to be significant for capsules (-2.28%, 95% CI -2.60, -1.96) and patches (-0.48%, 95% CI -0.64, -0.32).

The median durations of TTh formulations were 68 months for injectables, 90 months for capsule, 90 months for gel, and 60 months for patch.

Patterns in serum testosterone testing

Initial serum testosterone measurements are used to provide a biochemical diagnosis supporting clinical hypogonadism; this is considered a standard of care.[5-8] Post-TTh, serum testosterone measurements are recommended to ensure appropriate dose titration of TTh.[5-8] During this study period, the percentage of men in whom serum testosterone tests (either total or free) were drawn within one year prior to their first prescription rose from 69% in 1998 to 85% in 2013 (Fig. 3A). This represented a significant linear trend, with a percentage increase of 1.27% (95% CI 1.06, 1.48) per year. The percentages of post-prescription measurements rose from 20% in 1997 to 51% in 2012, for a cumulative rate of post-TTh testing of 36% (12 539 of 34 582 men overall). The observed linear trend was significant, with a percentage increase of 2.09% (95% CI 1.85, 2.34) per year. Most men started TTh treatment soon after being tested (median duration, defined as date of closest pre-treatment serum testosterone test to date of first TTh=19 days) (Fig. 3B), while there was a longer amount of time for the post-serum testosterone draw (median duration, defined as date of first TTh to closest post-treatment serum testosterone test=87 days).

Percentages of total testosterone measurements for men with matching same-day MSP codes were categorized as low (<9 nmol/L), borderline (9–<12 nmol/L) or normal (12–28 nmol/L) (Fig. 4). Between 2009 and 2010, there was a significant increase in the percentage of low pre-treatment tests and an accompanying decrease in normal and borderline pre-treatment tests.

For those men who had low pre-TTh serum testosterone measurements, 49% remained low post-TTh and 51% became borderline or normal/high post-TTh (Table 1). Curiously, 26% of men with borderline and 11% with normal testosterone at baseline actually had low levels after starting therapy.

Prescribing physicians

From 2008–2013, there were increasing counts of TTh prescriptions; these were mostly written by general practitioners, followed by urologists, internal medicine physicians, and endocrinologists (Table 2).

In terms of percentage of physician prescriber type ordering a pre-TTh serum testosterone test, general practitioners displayed a significant percentage increase of 1.39% per year (95% CI 1.17, 1.61) over the course of the study, while increases for urology and internal medicine were 0.47% (95% CI 0, 0.93) and 0.93% (95% CI 0.06, 1.81), respectively. Trends for endocrinologists were not significant (Fig. 5A). For post-TTh serum testosterone tests, percentage increases for general practitioners (2.01%, 95% CI 1.75, 2.27), urology


Fig. 1C. Distribution of first testosterone therapy (TTh) prescription by age (n=37 741 men).
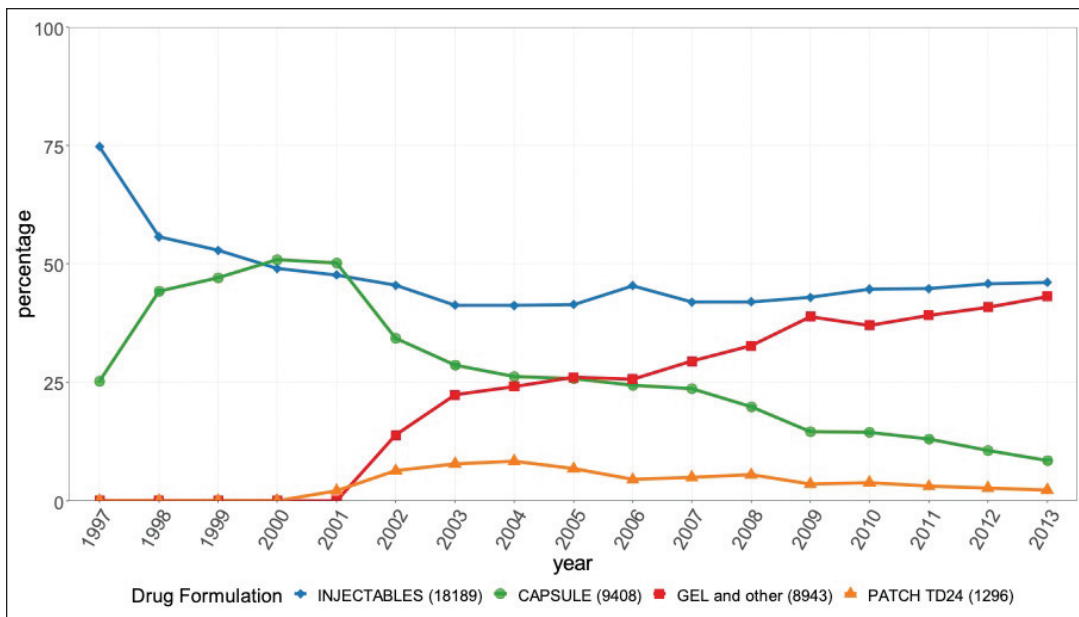
Fig. 2. Distribution of treatment types at first testosterone therapy by year. *Prior to 2001, there were only two treatment types used (injectables and capsule), after which gel and patch formulas became options for patients.

(3.26%, 95% CI 2.82, 3.69), and internal medicine (2.11%, 95% CI 1.47, 2.76) were significant. General practitioners consistently ordered fewer labs as compared to urologists, internal medicine, and endocrinologists (Fig. 5B). The median duration of prescription was longest when prescribed by endocrinologists (120 months) and shortest when prescribed by general practitioners (70 months) (Table 2).

Discussion

Our analysis of 37 741 men revealed that the number of men prescribed testosterone in BC has increased 1.57-fold from 1998–2013, with a steeper increase in the trend after 2008. The magnitude of trend from 2008 onwards was similar to that observed in the U.S. over a similar time period (3–8-fold),[1,3,4] and may be related to the availability of transdermal testosterone formulations (i.e., gel and patch).
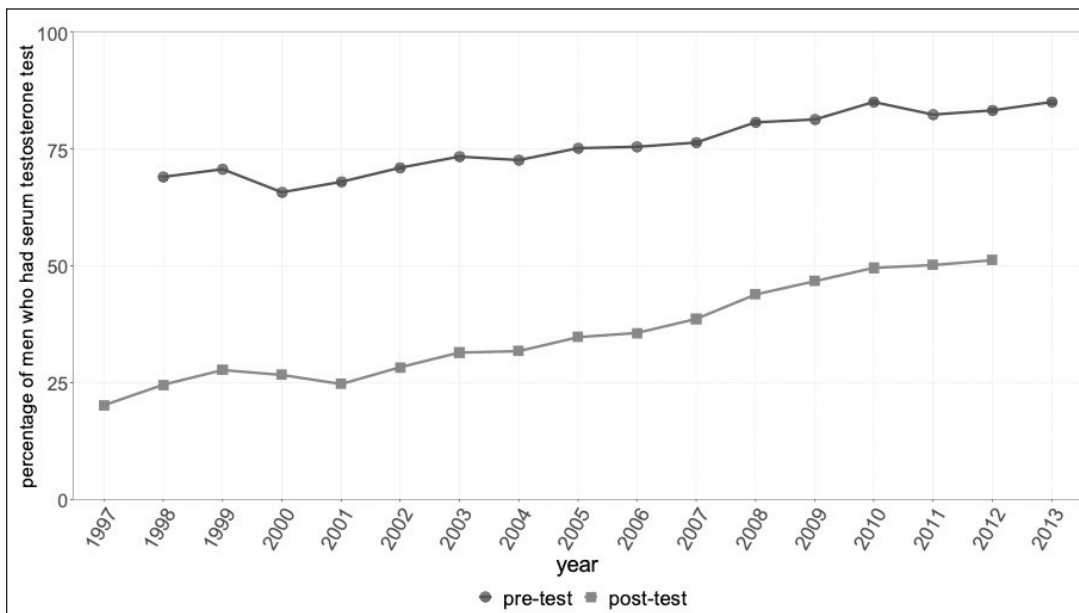
Fig. 3A. Percentages of pre- and post-testosterone therapy serum testosterone tests performed within a one-year time-window of first prescription. *The pre-treatment test curve starts in 1998 to allow capture of pre-treatment tests in the previous year. The post-treatment test curve ends in 2012 to allow capture of post-treatment tests in the last year of the study period.
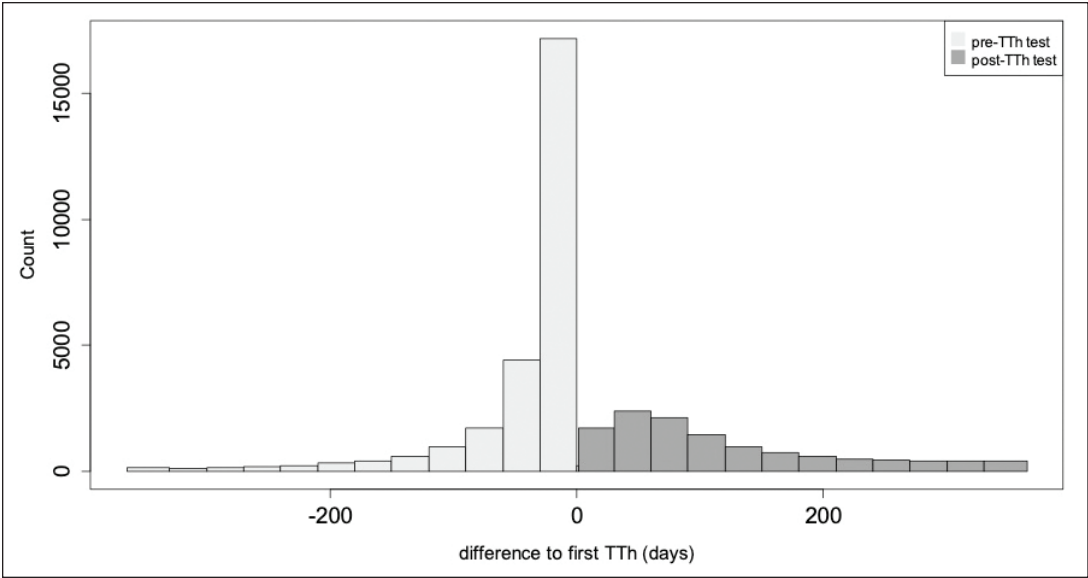
Fig. 3B. Distribution of the time interval of pre- and post-serum testosterone measurement relative to the date of first testosterone therapy (TTh) prescription within a one-year time window.

Injectables were the most prescribed form of testosterone replacement therapy from 1998–2013; however, there was an expected rise in gels when they came to market. We note that most recent American College of Physicians guidelines favor the use of intramuscular rather than transdermal formulations to improve sexual function at a lower cost with similar clinical effectiveness and potential harms.[8] Other international guidelines do not specify best prescription type.[5-8] As such, various options for TTh are available with varying strengths and weaknesses, and likely require

individualized treatment approaches based upon patients' needs and preferences.

Despite median duration of therapy ranging from 70–120 months, nearly half of all men only filled 1–3 prescriptions, suggesting willingness to trial but not continue therapy. This pattern may be due to inadequate response or unwanted side effects. Investigating this further, we found that among men with low pre-TTh serum testosterone levels, half remained low following TTh, while only 37% obtained a normal serum testosterone level. Furthermore, 37% of men with borderline
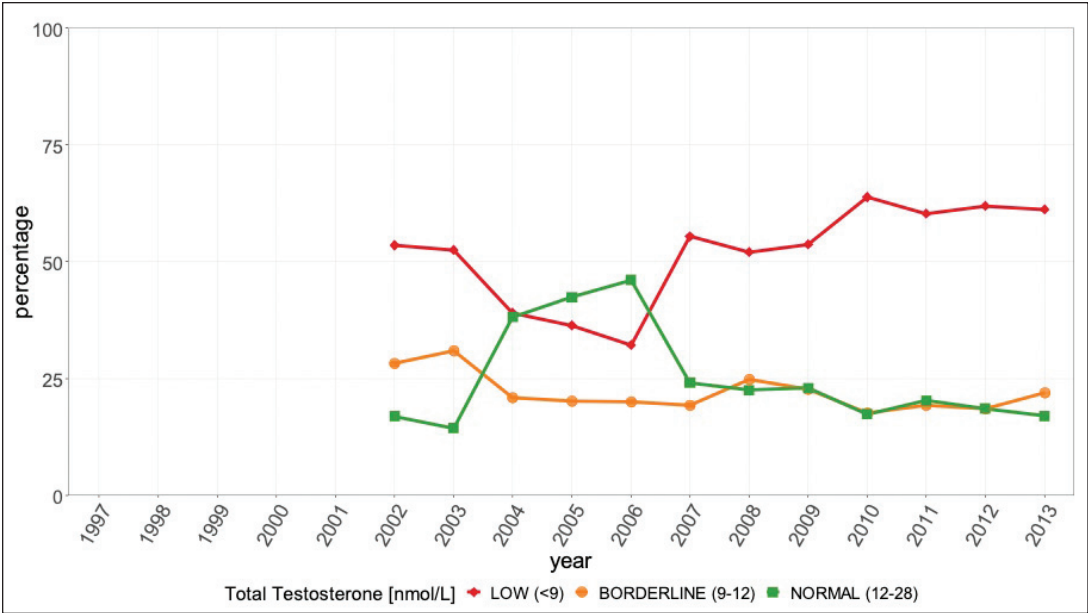
Fig. 4. Percentage of total testosterone measurements for men with matching same-day MSP codes were categorized as low (<9 nmol/L), borderline (9–<12 nmol/L) or normal (12–28 nmol/L).

Table 1. Summary of absolute counts and percentages of men with low, borderline, normal, and high serum total testosterone levels pre-TTh (rows) and post-TTh (columns) testing

	Low (post)	Borderline (post)	Normal (post)	High (post)	Total count
Low (pre)	263 (49%)	76 (14%)	163 (30%)	40 (7%)	542
Borderline (pre)	39 (26%)	31 (21%)	61 (41%)	19 (13%)	150
Normal (pre)	14 (11%)	22 (17%)	81 (61%)	15 (11%)	132

There were only six men with a total testosterone pre-TTh level in the high category and they were excluded in the table. TTh: testosterone therapy.

or normal serum testosterone levels pre-TTh were found to have low levels post-TTh. This may be due to the timing of lab testing occurring during a trough level or to the exogenous dosing negatively regulating pituitary production of luteinizing hormone, through the classically described negative feedback mechanism.[13] This would result in minimal testicular testosterone production, while exogenous doses were inadequate to fully support eugonadal levels. Other investigators have not found a correlation between the relief of hypogonadal symptoms and pre-TTh serum testosterone levels,[14] emphasizing the requirement for proper dose titration guided by serum levels post-TTh.[5-8] Further studies are required to better optimize the timing of post-TTh serum testosterone testing (peak, trough, or mid-cycle).

Not surprisingly, the most common prescribers of TTh in Canada are general practitioners, followed by urologists and internists. Our analysis showed comparable prescribing patterns of practice between the various physician groups. Although Canadian general practitioners were the major drivers of the overall increase in the number of serum testosterone measurements taken prior to prescribing testosterone (1998–2013), the situation differed for post-prescription serum testosterone levels, as the number of general practitioners requesting this measurement did not increase in proportion to other prescribers, particularly urologists (1997–2012). Furthermore, median duration of prescription was shortest when prescribed by general practitioners. Improving education of general practitioners on the importance of ordering post-TTh serum testosterone levels, as well as optimal dose titration methods may help address the observed low compliance of TTh.

A limitation of our study was the challenge of accessing all the actual serum testosterone measurement values from data provided by Population Data BC. However, the data that documented ordering of a serum testosterone test was complete, as it was completely captured in the MSP database. This allowed for an albeit smaller, but accurate subgroup analysis to evaluate the measured testosterone levels.

Also, measurement of serum testosterone values following TTh is complicated by the variability due to timing relative to dose administration (i.e., trough, peak, mid-cycle) in men on injectable drugs and we chose to focus on the first testosterone measurement following TTh prescription; thus, it is possible that with subsequent and different timing of testing, testosterone values may have responded differently over time. Lastly, in our databases we do not have access to patients' hypogonadal symptoms (presence and degree), and so could not assess clinical response to treatment. Lastly, we cannot determine with certainty whether lack of post-TTh testing was due to physician practice or patient compliance.

Conclusions

Overall, the results of this study highlight significant deviations from standard-of-care for TTh prescribing in Canada. In particular, nearly half of the men do not remain on TTh for more than a short trial period. Adherence to guidelines on suggested monitoring of serum testosterone levels before and after initiation of TTh has improved, but rates remain unacceptably low, with only 36% of all the men receiving post-TTh serum testosterone monitoring. Among those being tested, approximately half of men with low testosterone prior to TTh remain low following therapy. We suggest that the absence of biochemical testosterone assessment both before and after treatment likely contributes to inappropriate prescribing, poor adherence, and inadequate therapeutic response. As a group, general practitioners were the least adherent to ordering post-TTh serum testosterone levels and, thus, may benefit from future directed educational initiatives. Further studies must also address the issue of optimizing the timing of serum testosterone level measurements, considering we found significant variations in pre- and post-TTh serum testosterone levels. Overall, clinician education is required around TTh prescribing, dose titration, and monitoring to ensure both effective and safe prescribing practice.

Table 2. Distribution of prescriber types by median duration of TTh prescription

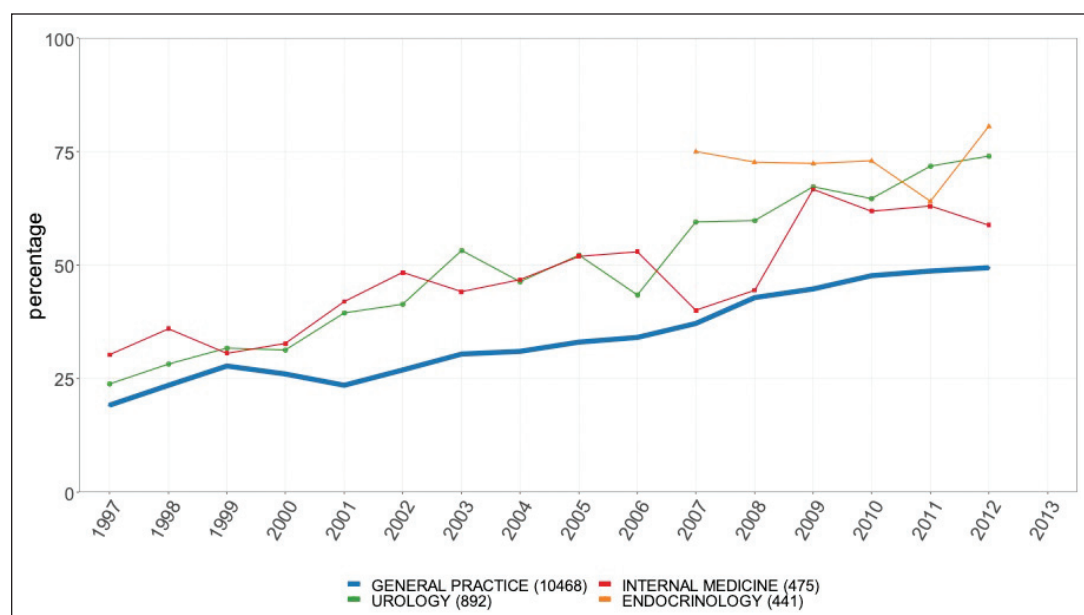| Prescriber type	General practice	Urology	Internal medicine	Endocrinology	Other
Number of first TTh	32 739	1991	1152	720	405
Median duration (months)	70	90	101.5	120	90

TTh: testosterone therapy.
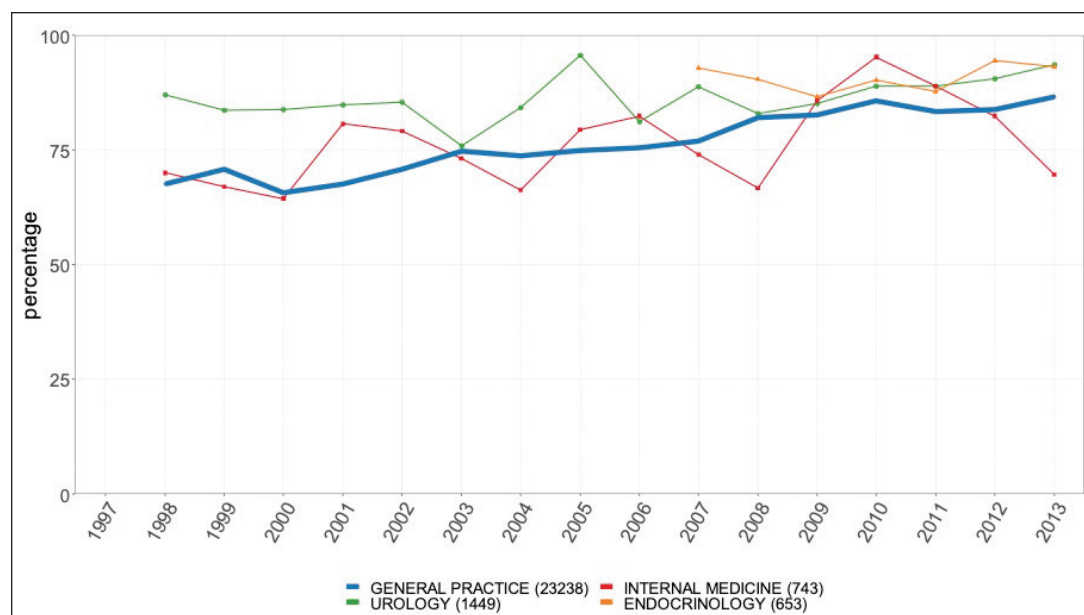
Fig. 5A. Percentage of each practitioner type that are ordering a pre-testosterone therapy (TTh) serum total testosterone measurement (n=26 083 first TTh) as analyzed on an annual basis from 1998–2013.

Fig. 5B. Percentage of each practitioner type that are ordering a post-testosterone therapy (TTh) serum total testosterone measurement (n=12 276 first TTh) as analyzed on an annual basis from 1997–2012.

References

1. Elliott J, Kelly SE, Millar AC, et al. Testosterone therapy in hypogonadal men: A systematic review and network meta-analysis. *BMJ Open* 2017;7:e015284.
2. Diem SJ, Greer NL, MacDonald R, et al. Efficacy and safety of testosterone treatment in men: An evidence report for a clinical practice guideline by the American College of Physicians. *Ann Intern Med* 2020;172:105-18. https://doi.org/10.7326/M19-0830
3. Baillargeon J, Kuo YF, Westra JR, et al. Testosterone prescribing in the United States, 2002–2016. *JAMA* 2018;320:200-2. https://doi.org/10.1001/jama.2018.7999
4. Layton JB, Li D, Meier CR, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000–2011. *J Clin Endocrinol Metab* 2014;99:835-42. https://doi.org/10.1210/jc.2013-3570
5. Morales A, Bebb RA, Manjoo P, et al. Diagnosis and management of testosterone deficiency syndrome in men: Clinical practice guideline. *CMAJ* 2015;187:1369-77. https://doi.org/10.1503/cmaj.150033
6. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol* 2018;200:423-32. https://doi.org/10.1016/j.juro.2018.03.115
7. Lunenfeld B, Mskhalaya G, Zitzmann M, et al. Recommendations on the diagnosis, treatment, and monitoring of hypogonadism in men. *Aging Male* 2015;18:5. https://doi.org/10.3109/13685538.2015.1004049
8. Qaseem A, Horwitch CA, Vijan S, et al. Testosterone treatment in adult men with age-related low testosterone: A clinical guideline from the American College of Physicians. *Ann Intern Med* 2020;172:126-33. https://doi.org/10.7326/M19-0882
9. Central stats agency: Population Estimates, BC Stats, central statistical agency of the Province of British Columbia 2015.
10. Canadian Institute for Health Information [creator] (2014): Discharge Abstract Database (Hospital Separations). V2. Population Data BC [publisher]. Data Extract. MOH (2014). Available at: http://www.popdata.bc.ca/data. Accessed July 27, 2020
11. British Columbia Ministry of Health [creator] (2010): Medical Services Plan (MSP) Payment Information File. V2. Population Data BC [publisher]. Data Extract. MOH (2010). Available at: http://www.popdata.bc.ca/data. Accessed July 27, 2020
12. British Columbia Ministry of Health [creator] (2013): PharmaCare. V2. Population Data BC [publisher]. Data Extract. MOH (2013). Available at: http://www.popdata.bc.ca/data. Accessed July 27, 2020
13. Bagatell CJ, Dahl KD, Bremner WJ. The direct pituitary effect of testosterone to inhibit gonadotropin secretion in men is partially mediated by aromatization to estradiol. *J Androl* 1994;15:15-21.
14. DeFina LF, Radford NB, Leonard D, et al. Traditional signs and symptoms commonly attributed to hypogonadism do not correlate with testosterone levels: The Cooper Center Longitudinal Study Experience. *J Investig Med* 2020;68:378-82. https://doi.org/10.1136/jim-2019-001083

Correspondence: Dr. Ryan Flannigan, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada; ryan.flannigan@ubc.ca