Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2014 May ; 23(5): 498–506. doi:10.1002/pds.3579.

Population-based patterns of prescription androgen use, 1976-2008

Susan A. Hall, Ph.D.¹, Gayatri Ranganathan, M.S.¹, Liane J. Tinsley, M.P.H.¹, Jennifer L. Lund, Ph.D.², Varant Kupelian, Ph.D.¹, Gary A. Wittert, MBBch, MD³, Philip W. Kantoff, M.D.⁴, Alvaro Morales, M.D.⁵, and Andre B. Araujo, Ph.D.¹

¹Department of Epidemiology, New England Research Institutes, 9 Galen St., Watertown, MA, 02472 USA

²Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark

³Discipline of Medicine, University of Adelaide, SA 5005 DP509 Australia

⁴Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston MA 02215 USA

⁵Department of Urology, Queen's University, 62 Barrie St. Kingston, ON, K7M 6R4 Canada

Abstract

Purpose—Prescription testosterone (T) has limited approved medical indications and is a controlled substance in Canada. Utilization studies in other Westernized countries have revealed sharp increases in T use in recent years. We examined medical use of androgens, including T, over a 30 year period among adult (18+) men in a population-based study set in a Canadian jurisdiction of universal health care.

Methods—Analyses were based on data from electronic records of dispensed prescriptions during 1976-2008 in Saskatchewan, Canada. All formulations of androgens listed in the provincial formulary (oral and injectable) were included. We examined demographics of users, androgen types used, switching patterns, and trends in the annual rate of use over time.

Results—There were 11,521 androgen users who were followed for an average of 11.8 years. Overall, 11 types of androgens were used and there were 86,812 dispensing events. The mean age at first use was 56.4 years (median: 58). Men had 7.5 prescription dispensing events on average (median: 2). The most commonly-used formulations were methyl-T (36.2% of users) followed by T-enanthate (32.5%), T-cypionate (22.3%) and T-undecanoate (20.0%). Most users (82%) did not switch among androgen types. The annual rate of use varied substantially over time, with a marked increase observed from 1994-1999 and a decrease from 2000-2008.

Conclusions—Androgen users were largely middle-aged and had relatively few dispensings. We hypothesize that observed secular trends in androgen use may align with drug treatment

¹**Corresponding Author:** Susan Hall, New England Research Institutes, 9 Galen St., Watertown, MA 02472; (tel) 617 923 7747; (fax) 617 924 0968, shall@neriscience.com.

AUTHOR POTENTIAL CONFLICTS OF INTEREST: Dr. Lund reports being reimbursed as a consultant for GlaxoSmithKline, LLC for research services unrelated to the current study. Dr. Wittert reports research support from Bayer Schering and Eli Lilly. Dr. Wittert serves on an international advisory board and a local advisory board for Eli Lilly as well as receives speaker fees from Eli Lilly. Dr. Wittert also is a consultant to and a contract researcher for Lawley Pharmaceuticals. Finally, Dr. Wittert has received research funding from the National Health and Medical Research Council. Dr. Araujo has consulted with Lilly USA LLC and has received research support from GlaxoSmithKline and Abbott Laboratories. Drs. Hall, Kantoff, Kupelian, Morales, Ms. Tinsley and Ms. Ranganathan have no potential conflicts of interest.

pattern changes for erectile dysfunction (ED), including the advent of phosphodiesterase type 5 inhibitors.

Keywords

androgens; testosterone; drug utilization; hypogonadism; pharmacoepidemiology

Introduction

Prescription testosterone (T) has a narrow range of approved medical indications and is a controlled substance in Canada and elsewhere due to its potential for misuse and abuse. While the drug has been available in the United States (U.S.) for more than 70 years, utilization patterns have recently changed. Use in the U.S. has increased three-fold among men aged 40 and older during 2001-2011.¹ It has been noted that an increase is occurring in the context of evidence for illegal use,² as well as in the absence of changes in recommendations for use³ (e.g., an expansion of approved indications). Prostate cancer and cardiac events are the primary safety concerns associated with use of exogenous T.⁴⁻⁶ Given these concerns, population-based patterns of use over time are needed. There is a growing body of literature on national patterns of testosterone utilization,^{1,3,7,8} and characteristics of users.^{1,9-13} To our knowledge, no study of more than two years' duration has been conducted in Canada.¹⁴

Our objective was to conduct a population-based prescription drug utilization study to examine medical use of androgens (including T) among adult (18+) men in a single Canadian province: Saskatchewan, a jurisdiction of universal health care. Our goals were to describe demographic and medical characteristics of users, number of dispensed prescriptions per patient, switching patterns within androgen types, and utilization changes over time. To fulfill these objectives, we used linked administrative records from Saskatchewan for a period of approximately 30 years in a retrospective cohort design.

Materials and Methods

Study approvals

The study was approved by The University of Saskatchewan Biomedical Research Ethics Board, the Saskatchewan Ministry of Health's Data Access Review Committee, and exempted by New England Research Institutes' Institutional Review Board.

Study setting

The province of Saskatchewan, Canada is a discrete jurisdiction of universal health care for all ages. Only those whose health care is federally funded, including federal inmates, members of the Royal Canadian Mounted Police, and armed forces (<1% of the Saskatchewan population), are excluded from provincial health care coverage.¹⁵ In 2004, the covered population was 1,018,057 (49.7% men).¹⁶ Among covered persons, all are eligible for prescription benefits from the provincial Drug Plan except for approximately 9% of residents whose medications are paid for by a different public source (primarily First Nations members). The provincial Drug Plan operates in a formulary, which lists those medications eligible for coverage; medications not listed in the Saskatchewan Formulary are ineligible for coverage but may still be prescribed and dispensed within the province.

Data sources

Electronic databases secondary to this health care are available for research purposes and include prescription drug information, physician visits, characteristics of the covered

population, hospitalization data, a cancer registry, and vital statistics. These data are a recognized resource for drug utilization and other pharmacoepidemiologic studies.¹⁷ This analysis was based on data from electronic records of dispensed prescriptions eligible for Drug Plan benefits (i.e., listed in the Drug Plan's formulary) in the province from 1976-2008 (the totality of available benefit data). Available information includes dispensing date, medication quantity, and specialty of prescriber. Refilled prescriptions are included in dispensings. Each patient in the drug database has a unique identification number that may be linked to information in other databases allowing for observation of longitudinal prescription histories. Indication and directions for use (i.e., how many to take daily) for each dispensing are not available. Over the 32-year study period, prescription drug data are incomplete for an eighteen-month period (July 1987-December 1988) due to administrative changes.¹⁶ Adult men (aged 18+) were the research focus as the dataset was constructed for the purposes of analyses of risk considering androgen use and subsequent prostate cancer.

Additional aggregate data based on nonbenefit medications (i.e., not eligible under the Drug Plan) dispensed in the province were compiled and provided to the authors by the Saskatchewan Ministry of Health. The Ministry of Health began capturing all dispensed prescriptions in the province regardless of eligibility in 2006. These data were available only for a small proportion of our study years (2006-2008) and contained number of users and dispensings of topical formulations of androgens (gel and patch delivery). These data were not provided at the individual user level and therefore could not be combined with our study dataset, but were used to help interpret possible explanations for utilization trends.

Androgens

All androgens listed in the Saskatchewan Formulary over the study years were included in the study.¹⁸ Topical formulations (e.g. gels, patches) and injectable T-undecanoate were not listed in the Formulary (i.e., ineligible for coverage but still prescribed and dispensed in the province) during the study period. Pellet formulations are not approved for use in Canada. In the Formulary, there were four injectable and seven orally-administered androgens. Injectables included testosterone cypionate (T-cypionate), testosterone enanthate (T-enanthate), nandrolone decanoate, and nandrolone phenpropionate. Oral formulations included fluoxymesterone, methandrostenolone, methyltestosterone (methyl-T), norethandrolone, oxymetholone, stanozolol, and testosterone undecanoate (T-undecanoate). Initial treatment by androgen type and subsequent changes were noted. Regarding days' supply dispensed, a pharmacist may claim one dispensing fee for each 34-day supply. This rule is most amenable to oral dosage forms and certain deductions can be made about days' supply based on the quantity (e.g., number of tablets) dispensed. However, such deductions are not as reasonable when it comes to parenteral dosage forms. This is complicated further when a particular product can be dispensed as either a single-use ampoule or a multi-dose vial. Because the amount dispensed was not standard for each androgen type, we used number of dispensing events as a proxy for duration of use.

Approved indications and contraindications for androgens in Canada and prescribing guidelines

Although prescribing 'recommendations' for Canada exist,¹⁹ there are no medical society practice guidelines for androgen prescribing in Canada¹⁴ as in other regions (e.g., Europe,²⁰ U.S.²¹). According to current prescribing monographs available at the Health Canada website, approved indications for androgens in men are, "...conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism)" with further comment, "...should not be used to treat non-specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other etiologies responsible for the symptoms have not been excluded." A history of breast cancer, prostate cancer, use in

persons <18, and use in women are contraindications. Use in hypertensive patients and men aged 65+ are included as warnings/precautions.²²

Eligibility for analytic sample

Covered men with prescription benefits were included in the study if they had a first androgen prescription dispensing on or after their 18th birthday, no history of prostate or breast cancer, and the dispensing date was during the study period (January 1, 1976 to December 31, 2008). The first dispensing noted in the patient record was assigned as date of first use. Because androgen type used first was of research interest, men were required to have at least one year of coverage in the database prior to first use in order to best identify first use (this was possible at all times except for men who were first users in January-August 1976, as the drug plan was introduced on September 1, 1975; this use was presumed to be first use). Users who had <1 day follow-up time (cohort entry and exit on same day) were excluded from analyses; these men comprised <0.05% of users. Men were followed from date of first use until a censoring event (death, end of study period, or health coverage termination).

Covariates

Age at first and last androgen use was derived from year of birth and dispensing date. We used dispensing records of medications used in a 3-month window following and including androgen initiation date as a proxy for the presence of pre-specified medical conditions. Use of antidepressants, oral hypoglycemics and/or insulin, and antiretroviral agents were considered indicative of depression, diabetes, and HIV/AIDS, respectively. HIV/AIDS was of interest as androgens are sometimes used 'off-label' to counteract hypogonadism and muscle wasting secondary to HIV disease.²³ Use of cardiac glycosides, anti-arrhythmic agents, and nitrates were taken as evidence of 'other' cardiovascular conditions, while dispensed antilipemics agents were considered evidence for high cholesterol. Dispensing of antihypertensives (AHTs: angiotensin converting enzyme inhibitors, beta blockers, centrally active AHTs, direct vasodilators, angiotensin II receptor antagonists, alpha blockers, and calcium channel blockers) was assumed to indicate hypertension. We were unable to specifically capture the comorbidities testicular hypofunction (ICD-9: 257.1 and 257.2) and Klinefelter's syndrome (ICD-9: 758.7) (indications for testosterone use²²), or erectile dysfunction (ED) (ICD-9-CM/ICD-9: 607.84 and 302.72) using the parenthetical ICD codes because ICD-9-CM codes are not used and only three digits of the ICD-9 code are used in the medical services database.

Statistical analysis

In order to calculate the denominator for an estimate of the rate of androgen use per year, we used provincial data on the population registered for health care at the midpoint of each year, with further estimation of the yearly covered population of men aged 18+ who also had prescription benefits. In accordance with methodology recommendations from the Saskatchewan Ministry of Health, this was accomplished by subtraction of First Nations members from the total covered population estimate (such members are the largest group whose prescription benefits are paid by another federal source). For study years 1976-1983, only five-year age groups were available and the covered population denominator for men aged 18+ with prescription benefits was estimated using men aged 20+. The rate of androgen use was calculated by counting unique men who were ever users (numerator) divided by the estimated covered population with prescription drug benefits (denominator) for each year, with the resulting rate expressed per 1000 men per year.

The study dataset was analyzed using SAS v.9.2 (Cary, NC). Trend analysis of rates of androgen use was performed using the Joinpoint Regression Program version 4.0.1

(Statistical Research and Applications Branch, National Cancer Institute), which applies a 'joinpoint' to distinct line segments in order to denote changes in annual trend and allows significance testing of observed changes in annual trend.

Results

There were 11,521 adult male androgen users eligible for our analyses, among whom 86,812 androgen prescriptions were dispensed during the study period (Table 1). Users had 7.5 prescription dispensing events on average (median: 2); 89.9% were prescribed by a general practitioner. Men who were ever users of androgens had a mean of 11.8 (median: 10.1) years of observation time (considering androgen-exposed or unexposed time). The mean age at first use was 56.4 years (median: 58); greater than half (55.5%) were between the ages of 50-69 at first use, while 30.4% were 65 at first use (data not shown in table). During the 3-month interval at and following androgen initiation, the proportion of men who used medications indicative of comorbidities was highest for AHTs (28.4%), followed by antidepressants (9.9%) and diabetes medications (8.8%).

Eleven oral or injected androgens were used during the study period; types of androgens used varied substantially over time (Figure 1). The variety of types was greater during 1976-1983 as compared to later study years. After 1983, seven androgens (stanozolol, fluoxymesterone, norethandrolone, methandrostenolone, nandrolone phenopropionate, nandrolone decanoate, and oxymetholone) were not used or made up only a very small proportion of all androgens. Methyl-T was discontinued in Canada in 2001²² but comprised a large proportion of prescriptions until 1994, after which T-undecanoate began to be prescribed. T-cypionate and T-enanthate were dispensed in all study years, with the latter representing the largest proportion of all types from 1994 and later. By the late 1990s, T-undecanoate, T-enanthate and T-cypionate made up the vast majority of androgen types.

Considering 'ever use,' the most commonly-used androgens were methyl-T (36.2% of all users) followed by T-enanthate (32.5%), T-cypionate (22.3%) and T-undecanoate (20.0%); remaining types were used by <5% of all users (Table 2). Considering androgens most frequently used *first* (initiation), patterns were similar. Men most commonly initiated androgen therapy with methyl-T (33.9%), followed by T-enanthate (25.0%), T-cypionate (16.4%), and T-undecanoate (14.6%). The mean and median ages of men initiating on these types did not vary substantially (means ranged from 55.7 to 58.3 years). Men more frequently initiated with orally administered (57.9%) versus injected (42.1%) androgens and most users (81.6%) did not switch among androgen types over the study period (data not shown in table). The mean and median number of types used was 1.2 and 1.0, respectively (range: 1-6) (data not shown in table). Of the four most commonly-used androgens, men who initiated with T-cypionate were most likely to switch to any other formulation (27.5%), followed by T-enanthate (19.1%).

Figure 2 depicts trends in any androgen use (vertical bars) over time (ignoring type) as well as time trends over the 32-year study period (trends indicated by connecting lines). The annual rate of use ranged from 1.6 per 1000 in 1976 to a high of 4.6 per 1000 in 2000, with substantial variation over time and significant trends. Androgen use was non-significantly increasing for the first 3 years of the study period (1976-1978). The rate significantly declined by approximately 3.6% annually between 1978 and 1994. Beginning in 1994, the rate of use began to increase again (on average, by 24.7% annually) and reached its highest points in 2000-2001 (approximately 4.2 per 1000). The rate then decreased to 3.0 per 1000 by 2006, and continued to decrease until the last study year, when it returned to the rate of earlier years.

Topical androgens were not listed in the Formulary, but analysis of supplemental aggregate data for prescribed and dispensed nonbenefit drugs during 2006-2008 showed that there were only 145-260 users of topical androgens annually in the province.

Discussion

We examined oral and parenteral androgen use during 1976-2008 in a single Canadian province among a large population of adult men who did not have a history of prostate or breast cancer and who were first users at age 18 years. We believe this is the first large population-based study that includes characteristics of users by androgen type and patterns of use considering initiation and subsequent changes in androgen type over a lengthy study period. We found that use of four types dominated androgen 'ever use' and initiation (methyl-T, T-enanthate, T-cypionate, and T-undecanoate). The noted shift from a wider variety of androgens in earlier years to exclusively testosterone preparations in later years is likely due to changes in prescribing guidelines.²⁴ Overall, we observed that most men did not initiate with androgens until well into middle age, received androgens from a GP, received a median of only 2 dispensings, and did not switch among types. In Canada, a prior study of clinical monitoring before first androgen use among men in the province of Manitoba was conducted for the years 2001-2003. Results were similar to ours in that the majority of men were 50 at first use and the vast majority of androgens were prescribed in primary care; indication and comorbidities were not available in this study.¹⁴ It is noteworthy that in our study that approximately 30% of men were also using antihypertensives or were aged 65 or older at first use; current prescribing information suggests that androgens should be used with caution in these populations.²²

The annual rate of androgen use went through many changes from the 1990s onwards, including a pronounced increase (1994-1999) and a pronounced decrease (2000-2008). We hypothesize that these changes may align with changes in the treatment of ED during these intervals. An American study in the early 1990's noted that androgens were then used as empiric treatment for ED.¹¹ The noted increase after 1994 may be consistent with clinical practice changes following the July 1993 publication of consensus statement suggesting that hypogonadal men with ED may benefit from treatment with androgens.²⁵ Conversely, the decrease in rate of use after 1999 may be consistent with substitution of androgens with newly available oral treatments for ED (phosphodiesterase-5 [PDE-5] inhibitors, ex. sildenafil/ViagraTM) after their first availability in Canada in March 1999.²⁶ These medications have never been listed in the Saskatchewan Formulary for an ED indication,²⁷ restricting us from examining our hypothesis by looking at switches to PDE-5s; such medications are not captured in our benefit-based data. This is a limitation of our study. However, an examination of use in the non-benefit data for 2006-2008 showed that use of sildenafil in Saskatchewan was widespread, with approximately 6000 to 7000 users per year (approximately 6 to 7 fold higher than androgen use in the same years). As such, we speculate that ineligibility for benefit did not hamper uptake and potential substitution of PDE-5s for androgens, while recognizing this is not direct evidence for the decline in androgen use. In June 2006, Health Canada issued a position paper on use of testosterone and communicated with manufacturers that labeled indications akin to 'andropause' were not supported by clinical data and must be removed, which may have also contributed to the 2006-2008 decrease in rate of use.²⁸ It is also reasonable to speculate that the dip in androgen use after 1999 could be explained by substitution with new dermatologically administered products which were becoming available in Canada at that time, but which have never been listed in the Saskatchewan Formulary.²⁷ The analysis of supplemental data does not suggest this was the case, however, given low usage.

Previous studies examining secular trends in androgen use have mainly noted sharp increases over time. An analysis of Australian androgen prescription trends from 1992-2010 using two national databases observed that total prescribing of defined monthly units increased by 2.5 fold over the interval; the proportion of users was not determined.⁸ Year-by-year results were dissimilar to our results in that a sharp increase was noted as of 2000 and beyond, rather than our decrease. The Australian analysis also considered expenditure by product type. Substantial increases were noted for transdermal testosterone product expenditure following their introduction in 2000, while expenditures on most older types did not decrease commensurately, suggesting a pool of new users. In addition, long-acting injectable formulation expenditures increased based on the 2006 introduction of injectable T undecanoate (Reandron® 1000). These products were not listed in the Saskatchewan Formulary during our study years. A new study of testosterone prescribing in primary care in the United Kingdom (2001-2010) had similar results to Handelsman's with respect to prescribing increases.⁷ Dispensing increased 90% over the period, with even more marked increases (three-fold) noted for gel transdermal products and the injected T-undecanoate (365% increase) following their introduction in 2003 and 2005, respectively. The UK saw a corresponding drop in oral T-undecanoate as well nongel types of transdermal products, whereas prescribing of short-acting injections was stable over the interval. Finally, a new study of androgen use in an insured U.S. population (men aged 40) found a three-fold increase in androgen use and a five-fold increase in use of gel formulations during 2002-2011; this study also estimated that 50% of new users used androgens for 150 days and that ED was a common diagnosis among users (31.9%).¹

While this is a comprehensive study of androgen utilization in a specific jurisdiction in Canada and the first to estimate the annual population rate of androgen use, limitations are also present. Although we had supplemental aggregate data results for non-benefit use in the province for two of our study years, we are unable to capture the use of androgen products not listed in the Formulary in all study years. It has been suggested that observed increases in prescribing in other countries are related to pharmaceutical company promotional campaigns^{8,29} that may reach the public through websites regardless of the legality of direct-to-consumer advertising in that country.⁷ Direct to consumer prescription drug advertising is not legal in Canada, and the timing and impact of pharmaceutical company marketing to Canadian prescribers, or campaigns to increase 'disease awareness' among potential patients in Canada over the study period are difficult to determine. However, it is reasonable to suspect that these campaigns may have been a factor in increasing use, especially during and after the 1990s when they were having an influence in other countries.⁸ As described above, however, our data reflect both increases and decreases in use in the 1990s and beyond.

The lack of adequate information to capture indications for use of androgens is another limitation. We did examine the prevalence of having the diagnosis code of 257 with any extension (representing testicular dysfunction, containing both hypofunction and hyperfunction) during the 3-month window after and including the date of first androgen use. The prevalence of this non-specific three digit code was only 6.5%, but the conclusions that can be drawn from this about potential off-label use are currently limited by the lack of validation of the code against medical records. However, among 759 men in our broader dataset (containing users and non-users) who had the diagnosis of TD at study entry, 98.8% were androgen users, suggesting the code may have predictive potential and should be studied further. Also related to potential off-label use, we were unable directly examine diagnoses of ED at the time of first androgen use. An additional limitation is that indications for treatment, method of diagnosis, and information on directions for use (allowing calculation of days' supply) are not included in the dispensing record. Finally, our study is unable to capture illegal use by persons in the province.

Study strengths include linkage with demographic and medical information, large number of users, and reliance on electronic dispensing records. The latter are not subject to recall bias or non-response bias³⁰ as would be the case with patient self-report of drug use. Drugs distributed as physician samples or in hospitals are not included in the dispensed prescription records,¹⁵ but it is not expected that androgens would be used to a large extent in hospitals, or distributed as samples (given their status as a controlled substance). Although data are incomplete for an 18-month period, the 30+year duration of our study enables examination of trends over time. We excluded some men from our study cohort, but we do not expect these exclusions to affect provincial generalizability. Men who were first users as children are not captured, but the four main androgens are contraindicated in children according to current prescribing guidelines;²² our exclusions of a history of breast and prostate cancer are also contraindications. Finally, we did not rely on medical claims but relevant medications to capture comorbidity. It is recommended that physician service claim data be considered secondary but not primary evidence of disease.³¹

Despite its limitations, the marked trends noted in our analysis suggest that androgen utilization studies should continue to be performed in Canada and elsewhere in order to monitor trends in use and the characteristics of users. The rather short length of use (a median of 2 dispensings) argues against the likelihood of abuse for non-medical indications but it also is suggestive of issues of effectiveness for indication and acceptability. The duration finding may also suggest that use was not for organic/syndromic causes of hypogonadism, which require continuous androgen replacement. The advent of direct-to-consumer advertising for testosterone supplementation in the U.S. (with cross-border advertising in the printed or electronic media), the international availability of websites promoting supplementation, and an ongoing testosterone testing advertising campaign in Canada^{32,33} serve to increase the need for utilization monitoring.

Acknowledgments

The authors gratefully acknowledge Mary Rose Stang, Saskatchewan Ministry of Health, and Nicholas Dagincourt and Alicia Spector (both NERI). Written permission has been received from all named persons to be included in this acknowledgement.

FUNDING STATEMENT/FINANCIAL DISCLOSURE: Supported by Grant Number R21CA143170 from the National Cancer Institute. The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. This study is based in part on de-identified data provided by the Saskatchewan Ministry of Health. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan or the Saskatchewan Ministry of Health.

REFERENCES

1. Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS. Trends in androgen prescribing in the United States, 2001-2011. *JAMA Internal Medicine*. 2013 (citation forthcoming).
2. Beaver KM, Vaughn MG, Delisi M, Wright JP. Anabolic-androgenic steroid use and involvement in violent behavior in a nationally representative sample of young adult males in the United States. *Am J Public Health*. 2008; 98:2185-7. [PubMed: 18923108]
3. Handelsman DJ. Trends and regional differences in testosterone prescribing in Australia, 1991-2001. *Med J Aust*. 2004; 181:419-22. [PubMed: 15487956]
4. Brand TC, Canby-Hagino E, Thompson IM. Testosterone replacement therapy and prostate cancer: a word of caution. *Curr Urol Rep*. 2007; 8:185-9. [PubMed: 17459266]
5. Harman SM. Testosterone in older men after the Institute of Medicine Report: where do we go from here? *Climacteric*. 2005; 8:124-35. [PubMed: 16096168]

6. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010; 363:109–22. [PubMed: 20592293]
7. Gan E, Pattman S, Pearce S, Quinton R. A UK epidemic of testosterone prescribing, 2001–2010. *Clin Endocrinol (Oxf)*. 2013
8. Handelsman DJ. Pharmacoepidemiology of testosterone prescribing in Australia, 1992–2010. *Med J Aust*. 2012; 196:642–5. [PubMed: 22676880]
9. Hall SA, Araujo AB, Esche GR, et al. Treatment of symptomatic androgen deficiency: results from the Boston Area Community Health Survey. *Arch Intern Med*. 2008; 168:1070–6. [PubMed: 18504335]
10. Mulligan T, Frick MF, Zuraw QC, Stenhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006; 60:762–9. [PubMed: 16846397]
11. Cavanah SF, Jacobson JM, McIntyre T. Clinical use of androgenic steroids at a major medical center: who prescribes androgens and how well do they do it? *J Clin Pharmacol*. 1993; 33:253–8. [PubMed: 8463439]
12. Siyambalapitiya S, Jonsson P, Koltowska-Haggstrom M, Gaillard R, Ho K, Ross RJ. A cross-sectional analysis of testosterone therapies in hypopituitary men on stable pituitary hormone replacement. *Clin Endocrinol (Oxf)*. 2008
13. Purcell DW, Wolitski RJ, Hoff CC, Parsons JT, Woods WJ, Halkitis PN. Predictors of the use of viagra, testosterone, and antidepressants among HIV-seropositive gay and bisexual men. *Aids*. 2005; 19(Suppl 1):S57–66. [PubMed: 15838195]
14. Katz A, Katz A, Burchill C. Androgen therapy: testing before prescribing and monitoring during therapy. *Can Fam Physician*. 2007; 53:1936–42. [PubMed: 18000271]
15. Downey, W.; Stanton, SL.; Beck, P.; Osei, W.; Nichol, JL. Health Services Databases in Saskatchewan.. In: Strom, BL., editor. *Pharmacoepidemiology*. 4th edition. John Wiley & Sons, Ltd.; Chichester: 2005.
16. Saskatchewan Health. Research Services E, Research & Evaluation Unit, Population Health Branch. Saskatchewan Health; 2005. Saskatchewan Health Services Databases: Information Document..
17. Strom, BL.; Kimmel, SE. *Textbook of Pharmacoepidemiology*. John Wiley & Sons, Ltd.; Chichester: 2006.
18. Drug Plan and Extended Benefits Branch. On-Line Formulary. Government of Saskatchewan; 2013. at <http://formulary.drugplan.health.gov.sk.ca/>)
19. Morales A, Bella AJ, Chun S, et al. A practical guide to diagnosis, management and treatment of testosterone deficiency for Canadian physicians. *Canadian Urological Association journal = Journal de l'Association des urologues du Canada*. 2010; 4:269–75.
20. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *J Androl*. 2009; 30:1–9. [PubMed: 18772485]
21. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010; 95:2536–59. [PubMed: 20525905]
22. Drug Product Database Online Query. Health Canada; 2013. (at <http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp>.) [April 9, 2013]
23. Newshan G, Leon W. The use of anabolic agents in HIV disease. *International journal of STD & AIDS*. 2001; 12:141–4. [PubMed: 11231865]
24. Nieschlag, E.; Wang, CH.; Handelsman, D., et al. *Guidelines for the use of androgens in men*. World Health Organization; Geneva: 1992.
25. NIH Consensus Development Panel on Impotence. NIH Consensus Conference: Impotence. *JAMA*. 1993; 270:83–90. [PubMed: 8510302]
26. Canadian Adverse Drug Reaction Newsletter. Health Canada; 2000. [March 28, 2013]
27. Saskatchewan Formulary Books. [March 28, 2013] Government of Saskatchewan: Drug Plan and Extended Benefits Branch. 2013. (at <http://formulary.drugplan.health.gov.sk.ca/FormularyBooks.aspx>.)

28. Bain J, Brock G, Kuzmarov I, International Consulting G. Canadian Society for the Study of the Aging Male: response to health Canada's position paper on testosterone treatment. *J Sex Med.* 2007; 4:558–66. [PubMed: 17498097]
29. Gorricho J, Gavilan E, Gervas J. Marketing, not evidence based arguments, has probably increased testosterone prescribing. *BMJ.* 2012; 345:e6905. [PubMed: 23077358]
30. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol.* 2005; 58:323–37. [PubMed: 15862718]
31. Rawson NS, D'Arcy C. Assessing the validity of diagnostic information in administrative health care utilization data: experience in Saskatchewan. *Pharmacoepidemiol Drug Saf.* 1998; 7:389–98. [PubMed: 15073968]
32. Eggertson L. Brouhaha erupts over testosterone-testing advertising campaign. *CMAJ.* 2011; 183:E1161–2. [PubMed: 21969410]
33. Kermode-Scott B. Canadian regulators dismiss complaint about campaign publicising low testosterone. *BMJ.* 2011; 343:d5501. [PubMed: 21880681]

Key Points

- Prescription testosterone has limited approved medical indications and is a controlled substance. Population-based utilization studies in developed countries are needed to understand off-label use and signs of potential abuse.
- We examined medical use of androgens among adult men in a single Canadian province: Saskatchewan (a jurisdiction of universal health care) in order to describe demographic and medical characteristics of users, number of dispensing events per patient, switching patterns within androgen types, and changes in rate of use over 1976-2008.
- Overall, 11 types of androgens were used by 11,521 users, with 86,812 prescription dispensing events. The mean age at first use was 56.4 years (median: 58). Men had 7.5 dispensing events on average (median: 2). Androgens were primarily prescribed by general practitioners.
- The annual rate of use varied substantially over time, with a marked increase observed from 1994-1999 and a decrease from 2000-2008.
- Observed secular trends in androgen use may align with treatment pattern changes for erectile dysfunction (ED), including the advent of PDE-5 inhibitors during the study period.

*Six months of data used for 1987; all data missing for 1988.

FIGURE 1.

Androgen types used as a proportion of all androgens used among adult men, Saskatchewan, 1976-2008.* Ever use of an androgen type by a unique man is counted once. Each colored section of a bar represents the proportion of a specific type of androgen used as a proportion of all androgen types used by unique men in each calendar year (thus depicting secular trends in androgen types).

*Users were men who used androgens at least once in the calendar year. Denominators estimated using men aged 20+ for years before 1984.

FIGURE 2.

Users of androgens per 1000 adult men per year in province of Saskatchewan, 1976-2008.*

*Users were men who used androgens at least once in the calendar year. Denominators estimated using men aged 20+ for years before 1984.

TABLE 1

Use of androgens from Saskatchewan Formulary among adult men, Saskatchewan Health Services Databases, 1976-2008.

Characteristic	Androgen users N=11,521
Total prescription events, N	86,812
Prescriptions dispensed per user, mean $\pm$ SD (median)	7.5 $\pm$ 15.2 (2.0)
Prescriber, N (%)	
General practitioner	78069 (89.9)
Endocrinologist	1289 (1.5)
Urologist	2958 (3.4)
Other medical specialty	4419 (5.1)
All other	77 (0.1)
Age at first use, N (%)	
18-29	664 (5.8)
30-39	735 (6.4)
40-49	1741 (15.1)
50-59	3210 (27.9)
60-69	3176 (27.6)
70-79	1730 (15.0)
80+	265 (2.3)
Age at first use, mean $\pm$ SD (median)	56.4 $\pm$ 14.1 (58)
Age at last use, mean $\pm$ SD (median)	58.7 $\pm$ 14.0 (60)
Observation time in database, mean $\pm$ SD (median) years	11.8 $\pm$ 8.1 (10.1)
Comorbidities [*] , N (%)	
Depression	1140 (9.9%)
Diabetes	1017 (8.8%)
Hypertension	3273 (28.4%)
HIV/AIDS	23 (0.2%)
High Cholesterol	794 (6.9%)
Other cardiovascular conditions	736 (6.4%)

* The presence of comorbidities was determined by use of relevant medications for other listed conditions in a 3-month interval following first androgen use.

TABLE 2

Androgen types ever used, first used, route of administration, number of dispensings, and age at first use among 11,521 male users, Saskatchewan Formulary, Saskatchewan Health Services Databases, 1976-2008.

Type	Number (%) of ever users of this type	Route	Number (%) of users who initiated with this type	Mean $\pm$ SD (Median) number of prescriptions dispensed *	Number (%) of initiators who switched to any other type	Mean $\pm$ SD (Median) age at 1st use among initiators of this type
Methyltestosterone	4172 (36.2%)	Oral	3907 (33.9%)	6.0 $\pm$ 14.8 (2.0)	608 (15.6%)	58.3 $\pm$ 12.6 (60)
Testosterone enanthate	3741 (32.5%)	Injected	2879 (25.0%)	8.4 $\pm$ 15.3 (2.0)	551 (19.1%)	55.7 $\pm$ 14.0 (57)
Testosterone cypionate	2573 (22.3%)	Injected	1890 (16.4%)	7.5 $\pm$ 14.8 (2.0)	520 (27.5%)	56.3 $\pm$ 13.1 (57)
Testosterone undecanoate	2301 (20.0%)	Oral	1682 (14.6%)	11.4 $\pm$ 18.3 (4.0)	243 (14.4%)	56.4 $\pm$ 11.9 (56)
Stanozolol	526 (4.6%)	Oral	480 (4.2%)	3.3 $\pm$ 5.6 (1.0)	48 (10.0%)	51.6 $\pm$ 22.4 (58)
Fluoxymesterone	414 (3.6%)	Oral	348 (3.0%)	6.8 $\pm$ 14.7 (3.0)	77 (22.1%)	53.2 $\pm$ 15.6 (55)
Methandrostenolone	190 (1.6%)	Oral	180 (1.6%)	7.1 $\pm$ 13.7 (2.0)	44 (24.4%)	44.8 $\pm$ 22.1 (38)
Nandrolone decanoate	73 (0.6%)	Injected	44 (0.4%)	3.0 $\pm$ 3.6 (2.0)	10 (22.7%)	64.9 $\pm$ 16.3 (73)
Oxymetholone	47 (0.4%)	Oral	42 (0.4%)	5.4 $\pm$ 6.9 (3.0)	5 (11.9%)	65.7 $\pm$ 16.9 (73)
Norethandrolone	37 (0.3%)	Oral	36 (0.3%)	2.0 $\pm$ 2.1 (1.0)	1 (2.8%)	57.8 $\pm$ 18.4 (63)
Nandrolone phenpropionate	48 (0.4%)	Injected	33 (0.3%)	3.2 $\pm$ 3.2 (2.0)	10 (30.3%)	44.2 $\pm$ 21.3 (34)

* Analysis of dispensings among those who initiated with this type.