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ORIGINAL REPORT

Pharmacoepidemiology of testosterone: Impact of reimbursement policy on curbing off-label prescribing

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Abstract

Objectives: To estimate the impact on testosterone prescribing over 3 years following the 2015 tightening of Pharmaceutical Benefits Scheme (PBS) criteria.

Design: Analysis of testosterone prescribing data from PBS and private (non-PBS) sources between 2012 and 2018 covering 2015 change in PBS prescribing criteria.

Main outcome measures: New and total PBS testosterone prescriptions estimating usage by quarter analyzed by product type, patient age-group, indication and prescriber type. Total national testosterone prescriptions (private plus PBS) was verified from an independent data supplier (IQVIA).

Results: PBS usage peaked in 2014 declining by 30% in 2017-8 with PBS prescribing covering a fall from 97.6% by usage in 2014 to 74% in 2017-18 of all testosterone prescribing. The tighter 2015 PBS restrictions sustained the selective reduction in GP initiation of prescriptions for middle-aged men without pathological hypogonadism whereas specialist initiations and prescription for adult hypogonadism or pediatric/prepubertal indications were largely unaffected.

Conclusions: The tightening of PBS criteria from 1 April 2015 to curb off-label prescribing remained effective and selective over 3 years yet total national testosterone prescribing continued with little change, reflecting a shift to private prescriptions. The continuation of off-label testosterone prescribing for unproven indications suggests that long-term androgen dependence is created in men without pathological hypogonadism who commence testosterone. This highlights the need to avoid prescribing testosterone to men without pathological hypogonadism in the absence of sound evidence of efficacy and safety, the latter including the little unrecognized risks of long-term androgen dependency when trying to quit.

KEYWORDS

androgen deficiency, hypogonadism, pharmacoepidemiology, prescription, testosterone

1 | INTRODUCTION

The remarkable worldwide increase in testosterone prescribing over recent decades despite no new approved indications is well known.[1,2] Testosterone product sales increased 100-fold over three decades to reach $US2 billion annually in the early 2010s.[3] Globally, a progressive increase in testosterone usage per capita was evident over the first decade of the 21st century in 37 of 41 countries and all regions investigated. This included a 40-fold increase in Canada and 10-fold increases in USA of national testosterone usage per capita.[3] After a peak in 2013-14, there is evidence that testosterone prescribing has started to fall in Australia[1] and in the USA[4] following concerns about cardiovascular safety and lack of efficacy data. These concerns led to regulatory curbs including FDA safety warnings and mandated label

changes in 2014-5 [5] and tightening of Australian Pharmaceutical Benefits Scheme (PBS) criteria for subsidized testosterone prescribing in 2015.[1] As virtually all testosterone prescribing in Australia occurs via the PBS scheme that provides taxpayer subsidy of the drug cost, changes to PBS reimbursement rules have the impact of regulatory changes. While the immediate impact of the changes in PBS rules from 1 April 2015 was reported,[1,6] the present study aimed to investigate the longer-term impact of the change over 3 years of the tighter 2015 PBS regulations.

Key Points

- The known. A massive increases in world-wide testosterone prescribing occurred over recent decades without any new approved indications. In Australia excessive testosterone prescribing was driven mainly by prescribing for invalid indications initiated by GPs for middle-aged men without reproductive pathology ("LowT") raising concerns about cardiovascular safety and lack of proven efficacy. In 2015 PBS criteria were tightened with effective immediate to selectively curb prescribing for "LowT" while leaving prescribing for valid medical indications unhindered.
- The new. We report the impact over 3 years on testosterone prescribing, by patient age-group, product, usage and prescriber type, of the 2015 tightening of PBS prescribing criteria showing sustained, effective selectivity in reducing prescribing for off-label without reducing valid indications. However, total testosterone prescribing continued with minimal change through a switch to private (non-PBS) prescribing.
- The implications. Effective and selective curbing of testosterone prescribing for valid medical indications can be sustained. However, testosterone prescribing for men who commenced testosterone treatment without valid indications continues by switching to private (non-PBS) prescribing for ongoing testosterone treatment driven by iatrogenic androgen dependence. This highlights the need for caution for initiating testosterone treatment in men without reproductive pathology including warning about potential ongoing androgen dependence.

2 | METHODS

2.1 | Data sources

Testosterone prescribing data were obtained from three sources.

2.1.1 | PBS statistics online

Pooled dispensing data (at date of processing) combing the Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS) data (referred to subsequently as PBS data) on prescribed testosterone products and expenditure were obtained from the public website (http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp) in monthly format for the years 2012 to 2018.[1,7,8] This provided monthly data with the numbers of product units converted into monthly usage according the product-specific approved dosages using the methodology developed by the WHO Collaborating Centre for Drug Statistics Methodology (https://www.whocc.no) as described previously.[1,7,8] The PBS data was grouped into quarterly intervals to match the DUSC data.

2.1.2 | DUSC data

Complementary PBS data on dispensing (not accessible via the public website) were provided pro bono by the Drug Utilization Sub-Committee (DUSC) of the Pharmaceutical Benefits Advisory Committee (PBAC). This provided quarterly data on prescriptions dispensed from 2012 to 2018 according to whether the prescription was (a) for new or renewed treatment (new being defined by (i) the prescriber's statement that the patient had never had testosterone prescribed previously and (ii) no previous testosterone prescriptions since at least 2003-4 with look-back for each person of at least 8 years), (b) the indication for testosterone treatment (pediatric/pre-pubertal, adult hypogonadism, Low T), (c) age group (in deciles) of the patient and (d) the type of medical prescriber (GP, endocrinologist, other specialist). Under the PBS scheme authority mechanism, the indications for, and any prior testosterone prescriptions, must be stated to obtain a PBS authority prescription when telephone approval is sought. Prescriber type was classified into general practitioners (GP), endocrinologists and other specialists (includes paediatricians, urologists, sexual medicine specialists). The PBS data was analysed into three categories of indications (a) adult (post-pubertal, disorders of hypothalamus, pituitary or testes), (b) pediatric/pre-pubertal (micropenis, puberty induction, constitutional delay of growth or puberty) and (c) men aged 40 or over without pathological hypogonadism, referred to in this study as "Low T" but also known by various synonyms as "andropause," "late-onset hypogonadism," "viropause," "partial androgen deficiency due to ageing (PADAM)," "age-related hypogonadism," "functional hypogonadism" or "prescribing-by-the-numbers (PBN)." The DUSC prescription data extracted were subject to a health privacy restriction that individual cells of the data were censored if they contained fewer than 5 units which was considered to constitute a risk of an individual being identifiable. The analysis of censored cells showed a mean of close to 2.5 (private communication), so this estimate was used to impute all the data missing due to health privacy censorship.

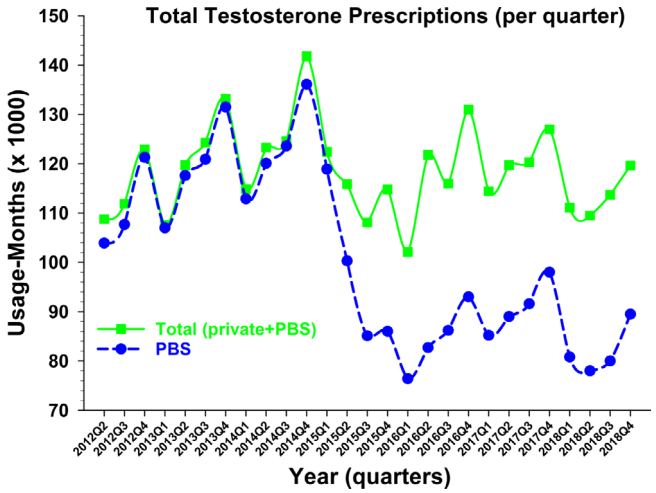

FIGURE 1 Testosterone prescribing from the years 2012 to 2018 (by quarters) showing usage (in patient-months per annum) with PBS data (blue filled circles, dashed lines) and IQVIA (green filled squares, solid lines), with the latter including total, that is PBS plus private non-PBS prescriptions

2.1.3 | IQVIA data

These data purchased from IQVIA (formerly IMS), an industry commercial supplier of wholesale drug sales to retailers (pharmacists), provided monthly data on all testosterone products sold in units and their cost from 2012 to 2018. The IQVIA data relates to sales of all testosterone products to pharmacies. As it combines private (non-PBS) and PBS prescriptions it represents total national testosterone sales. Pharmacies do not hold stocks of testosterone products (theft risk) and are supplied by wholesalers on a just-in-time daily delivery schedule so that wholesale sales data is a good surrogate for pharmacy dispensing of prescriptions. The IQVIA data was grouped into quarterly intervals to match available DUSC data. Health privacy restrictions dictated that the DUSC data arising from individual patient data could only be supplied when it met a censoring restriction that, for any data cross-tabulation supplied, no individual cell could contain less than five individuals. In such cases the cell was replaced with a missing data indicator to prevent the potential for identification of individuals whose data was being used.

New prescriptions for testosterone were distinguished from renewed prescriptions at an individual patient levels in the DUSC data. This was achieved because each individual application for a PBS prescription must state whether the patient has ever or never had testosterone prescribed previously. This indicator was verified by the patient not having a prior testosterone prescription since at least 2003-4 in an lookback for at least 8 years for each person.

Prior to 2015, any qualified doctor could prescribe testosterone under the PBS for men with a diagnosis of pathological hypogonadism (organic disorders of the hypothalamus, pituitary or testes that lead to life-long, irreversible inability to maintain adult male circulating testosterone levels[9] or for men without pathological hypogonadism who had at least two separate morning blood samples with serum testosterone lower than 8 nmol/L. From 2015 the PBS prescribing criteria required testosterone treatment be (a) initiated by consultation with a designated specialist (endocrinologist or other specialist) although testosterone treatment could be continued but not initiated by a GP, (b) for those without pathological hypogonadism ("LowT"), the low blood testosterone criterion was lowered to 6 nmol/L and (c) the low blood testosterone was not to be due to age, obesity, cardiovascular diseases, infertility or drugs.[1] The 2015 changes in reimbursement policy are outlined in the Figure S1.

TABLE 1 Changes in Pharmaceutical Benefits Scheme (PBS) and total testosterone sales and usage between 2014 and 2017-18

	2014	2017-18	Change
Usage (person-months, ×1000 pa)			
Total (IQVIA = private + PBS)	504.8	467.6	−7.4%
PBS	492.8	346	−30%
PBS as proportion of total	97.6%	74.0%	
Sales ($ million pa)			
Total (IQVIA = private + PBS)	23.6	20.8	−12%
PBS	20.2	13.6	−32%
PBS as proportion of total	86.0%	65.6%	

3 | RESULTS

PBS-based testosterone prescriptions decreased from 2015 according to usage whereas the total national prescriptions remained relatively stable over the period from 2012 to 2018 (Figure 1). Between the peak in 2014 and the average during 2017-8, total national testosterone usage and expenditure (Figure S2) by prescription decreased by 7.4% and 12%, respectively, whereas the PBS usage and expenditure decreased by 30% in usage and 32% in expenditure (Table 1). This divergence reflected the decreased proportion of all testosterone prescriptions covered by PBS, falling from 97.6% to 74% in usage (86% to 65.6% in expenditure) at those times.

The age group of patients newly prescribed testosterone within the PBS showed striking selective changes from 2015 onwards (Figure 2). Prior to 2015 over 80% of new prescriptions were for men from 40 years of age and older but after 2015 there was a striking 75% decline in this proportion for the years 2016-18. There was also a much smaller increase in new testosterone prescriptions for younger men, aged 10-30 years of age, which gradually increased in the years 2016 to 2018. Total testosterone prescriptions by age-group displayed similar directional changes although the magnitude of the changes were dampened reflecting that new prescriptions constitute only a low proportion (6.7%) of total prescriptions.

The indications for new testosterone prescription prior to 2015 included over 70% for "Low T" followed by nearly 30% for adult hypogonadism and only 2%-3% for pediatric/pre-pubertal indications (Figure 3). From mid-2015 onwards the numbers of new prescriptions for Low T dropped to virtually nil whereas the prescriptions for adult hypogonadism and pediatric/prepubertal indications remained

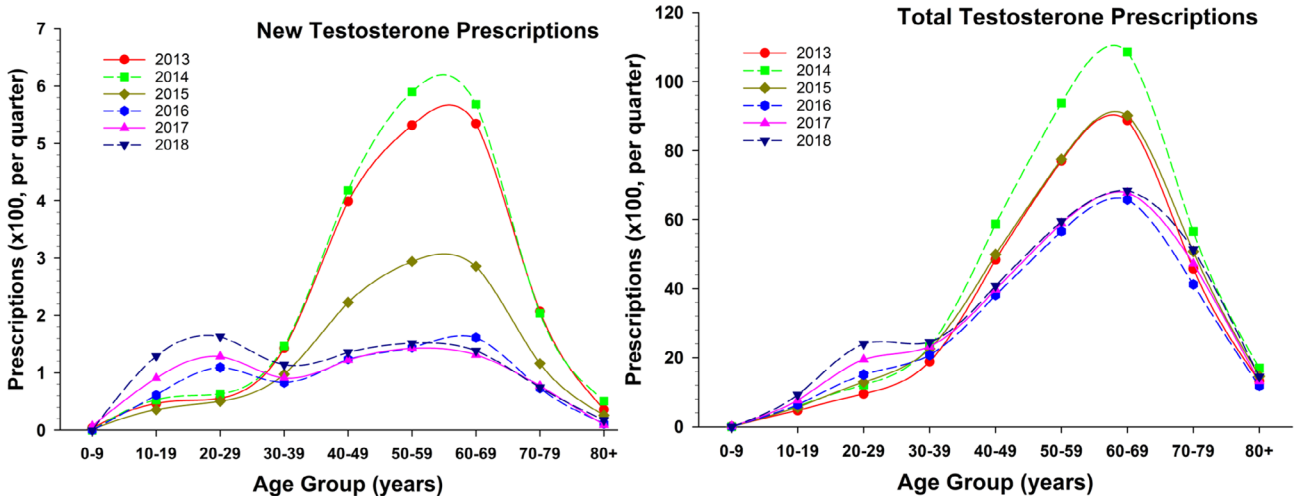

FIGURE 2 DUSC data on PBS testosterone prescription by age group (deciles of age) according to the year of the prescription from 2013 to 2018. The left panel depicts new prescriptions and the right panel depicts total (new plus renewed) prescriptions

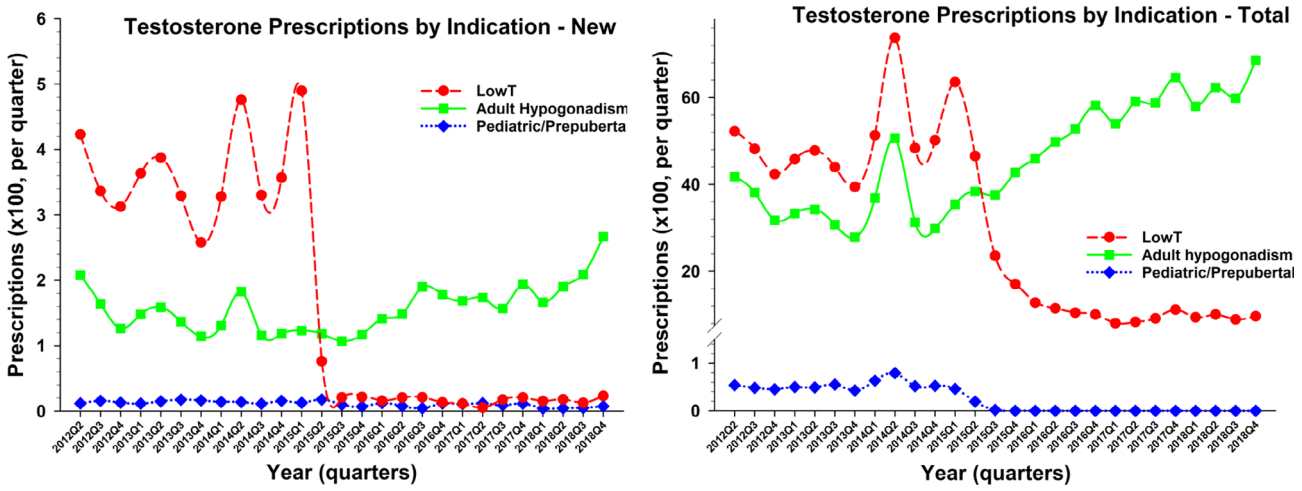

FIGURE 3 PBS testosterone prescription from 2012 to 2018 by quarter and by indication consisting of LowT (red filled circles, dashed lines), adult hypogonadism (green filled squares, solid lines) and prediatric/prepubertal (blue filled stars, dotted lines). The left panel depicts new prescriptions and the right panel depicts total (new plus renewed) prescriptions

unaffected and stable throughout the period 2012-8. Total testosterone prescriptions displayed similar patterns but dampened due to the low proportion of new vs ongoing renewed prescriptions.

Prior to 2015, the most frequent prescriber type was GP (75%) followed by equal proportions of endocrinologists and other specialists (Figure 4). From 2015 onwards GP initiations dropped to very low levels as mandated by the tightened 2015 PBS regulations. The numbers of new and total testosterone prescriptions by endocrinologists and other specialists was relatively stable throughout the 2012-18 period with a slight increase towards the end of the investigated period.

For specific product groups (injectable, transdermal) the temporal trends were generally consistent (Figure S3) with the proportion of total testosterone prescribing covered by PBS varying from 82% (long-acting) and 72% (short-acting) for injectables to 10% for transdermal products.

Within PBS, the number of new and total testosterone prescriptions (Figure S4) were stable between 2012 and 2014 but new prescriptions fell from 2015. Total PBS testosterone prescriptions remained relatively stable throughout the period 2012-2018 but new prescriptions fell by 75% from 2015 after which it remained stable at the lower level. Within PBS, new prescriptions formed 6.7% of total testosterone prescriptions.

4 | DISCUSSION

The present analysis shows that over the following 3 years, the 2015 tightening of PBS prescribing criteria to valid medical indications, subsidized testosterone prescribing fell from a peak in 2014 to stable lower levels while total national testosterone prescribing was largely

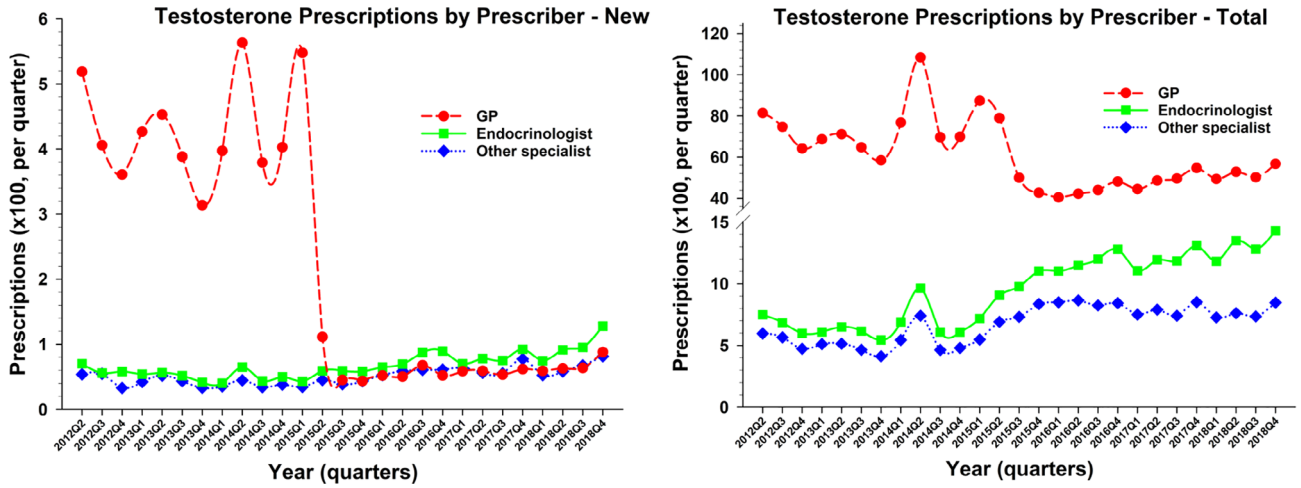

FIGURE 4 PBS testosterone prescription from 2012 to 2018 by quarter and by prescriber type consisting of GPs (red filled circles, dashed lines), endocrinologists (green filled squares, solid lines) and other specialists (blue filled stars, dotted lines). The left panel depicts new prescriptions and the right panel depicts total (new plus renewed) prescriptions

unchanged. This demonstrates that effective and selective targeting of PBS prescribing criteria to facilitate valid medical indications while curbing unjustified off-label testosterone prescriptions can be sustained without adversely affecting valid medical applications of testosterone.

A striking finding is that total testosterone prescribing remains largely unchanged at a national level despite restriction of PBS prescribing to valid medical indications. This ongoing testosterone usage involves men whose initiation onto testosterone treatment was not for valid medical indications but who switch to private non-PBS prescriptions after 2015 when subsidized prescriptions were no longer available. The financial burden of this switch is low for this old, long off-patent drug with the daily cost of testosterone products ($1-3/day) comparable with a cup of coffee, a cigarette or 1 day's charge for a mobile phone or internet connection. This continued use of testosterone most likely indicates androgen dependence in men who did not have pathological hypogonadism. Rather, they had intact hypothalamo-pituitary testicular axis that was suppressed by exogenous testosterone treatment through androgenic negative hypothalamic feedback effects. Hence, when exogenous testosterone intake stops, a transient state of androgen deficiency is created, with withdrawal symptoms lasting months[10] until normal reproductive axis function resumes. If men were not androgen deficient before starting off-label testosterone treatment (as usual), they will be androgen deficient when they stop. Such iatrogenic androgen dependence encourages continuation of testosterone treatment after the man chooses to quit treatment but is then driven to alleviate symptoms of androgen withdrawal. This is despite the fact that testosterone treatment further prolongs suppression of endogenous testosterone thereby delaying ultimate recovery and cessation of pointless testosterone treatment. This cycle of dependency makes it difficult to stop exogenous testosterone in men whose reproductive system was functionally normal when they start unjustified testosterone treatment (ie, without pathological hypogonadism). Such under-recognized iatrogenic androgen dependence may explain the analogous overcoming of previous regulatory curbs such as two episodes in Australia between 1994-6 and 2002-6 [7] and in Canada.[11]

The present analysis by age group and indications confirm the previous profile of patients prescribed testosterone prior to 2015[1,8] represent predominantly middle-aged men with a low circulating testosterone without disorders of the hypothalamus, pituitary or testes ("Low T," also known as "andropause" and late-onset hypogonadism"). These functional states differ from the adult hypogonadism or pediatric/pre-pubertal indications which represent pathological disorders of the male reproductive system (hypothalamus, pituitary, testis), the sole unequivocal and approved indication for testosterone treatment. By contrast, "Low T" represent an ad hoc aggregate of functional states with an adaptive down-turning of male reproductive activity by a healthy hypothalamo-pituitary-testicular axis in response to various systemic illnesses. Whether such adaptive reactions represent a beneficial, neutral or detrimental response requires rigorous evaluation by well-designed, placebo-controlled clinical trials evaluating efficacy and safety, which are almost entirely lacking.[12] The recent NIH-funded Testosterone Trials, a set of seven integrated studies prompted by a 2004 Institute of Medicine (IOM) report,[13] showed that for men over 65 years of age with LowT (but no reproductive disorders), daily treatment with testosterone gel compared with placebo produced a modest, transient increase in sexual function but no improvement in physical or cognitive function or vitality[14,15]; however, it also produced an increase in non-calcified coronary plaque, an unprecedented adverse surrogate marker of coronary disease.[16] These efficacy data did not warrant initiating testosterone treatment in older men without pathological hypogonadism[17,18] nor did they meet the mandate of the IOM report for sufficient short-term efficacy to warrant public funding for a large-scale clinical efficacy trial comparable to the Women's Health Initiative.[19] Overall "LowT" remains an invalid indication for testosterone prescription with the present study

highlighting the under-appreciated possible adverse effect of androgen dependence arising from such unjustified testosterone treatment.

The driving influences on testosterone prescribing for "LowT" include aggressive direct-to-consumer-advertising,[20] permitted in North America but not elsewhere, and disease-mongering clinical guidelines which elastically stretched the boundaries of a disease to expand sales of treatments.[12] For testosterone, the latter redefined the term "hypogonadism," defined as pathological disorders of the reproductive system, to encompass any conjunction of ubiquitous, non-specific symptoms with a low blood testosterone,[21] regardless of the underlying disease causing both and whether there was any causal link between symptoms and blood testosterone levels. In concert these factors led to phenomenal growth in global testosterone sales and usage.[3] This involves large numbers of men without reproductive disorders treated for a low serum testosterone (or sexual dysfunction) where efficacy remains unproven and possibly unsafe.[16,22,23] Conversely, the more recent abatement of excessive testosterone prescribing has been prompted by reports of possible adverse cardiovascular effects leading to regulatory curbs by the FDA and the PBS.[4]

This study has strengths and limitations. The strengths include a comprehensive national perspective on testosterone prescribing using both taxpayer-subsidized but restricted PBS as well as private data. It also avoids the ascertainment bias arising from more selective data sources such as insurance databases[4,24,25] or military health systems.[26-28] This study included complete information on the age group, indications and prescriber type related to individual testosterone prescriptions that explain the upsurge and abatement of excessive testosterone prescribing. This framework facilitates interpretation that changes in PBS rules led to a switch to private non-PBS prescriptions. The limitations include that the study lacked details of the underlying medical co-morbidities or clinical features that may have prompted testosterone prescribing.

It is concluded that the 2015 tightening of the PBS criteria for testosterone prescribing has had sustained, effective and suitably selective impact to curb unjustified off-label testosterone prescribing while not hindering testosterone prescribing for valid medical indications. The finding that total national testosterone prescribing continued largely unchanged after 2015 for men whose commencement of testosterone treatment was not medically justified is likely a manifestation of iatrogenic androgen dependence ultimately the result of having undertaken unjustified testosterone treatment. This highlights the need to restrict initiation of testosterone prescription to men with reproductive pathology and to exert caution and provide warnings to those with a functionally normal reproductive system which will become subject to iatrogenic, sustained suppression of endogenous testosterone with treatment by exogenous testosterone.

ETHICS STATEMENT

No ethical approval was required for this project as the available data contained no personal details. The PBS data is publicly available from the Medicare website (http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp). The IQVIA data refers to wholesale sales and the DUSC data had no personal reference. The DUSC data was supplied under confidentiality and health privacy censoring restrictions such that no cell of the cross-tabulated data could contain less than five individuals.

CONFLICT OF INTEREST

The author has received institutional grant (but no personal) funding for investigator-initiated testosterone pharmacology studies (Besins, Lawley) and has served as an expert witness at antidoping and professional standards tribunals and testosterone litigation.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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