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A National Analysis of Temporal Changes in Prescribing of Testosterone Replacement Therapy Considering Methods of Delivery and Government Regulation

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Purpose: Testosterone replacement therapy (TRT) is commonly used for various causes of androgen deficiency and subsidized by the Pharmaceutical Benefits Scheme (PBS) in Australia when appropriate. In response to a sharp increase in the prescribing of subsidized TRT, the Australian government instituted new, stricter prescription criteria in April 2015. We aim to demonstrate longitudinal changes in the prescription patterns of subsidized TRT over time.

Materials and Methods: The publicly available PBS database was accessed for TRT prescription data between 1992–2018. Population estimate data was collected from the Australian Bureau of Statistics for population-adjustment. Data analysis was performed according to class and specific formulation of TRT. Total and population-adjusted trends were considered, as was indexation to 2015 when restrictions were implemented.

Results: Longitudinal trends in subsidized TRT prescription demonstrated a progressive overall increase since 2000, according to total prescriptions and population-adjusted estimates, with greater use of topical formulations (gel, patch, cream/spray) and injections. Since 2015, a 37% decline in total population-adjusted prescriptions was observed (1,399–883 per 100,000 persons). Since 2015, relatively increased use of injections (50%) and 1% gel (30%) comprise the majority of contemporary TRT. Annual financial burden due to TRT was $AU16,768 per 100,000 persons prior to 2000 (mean cost 1992–2000), increasing to $AU112,539 in 2018 (due to use of injections). The rate of change in costs slowed after the restrictions were introduced in 2015.

Conclusions: The restrictions in subsidized TRT eligibility enforced by the PBS have reduced overall TRT prescriptions and slowed the cumulative financial burden.

Keywords: Androgens; Hormone replacement therapy; Hypogonadism; Testosterone

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INTRODUCTION

Since its first use in 1937, shortly after its Nobel prize winning discovery, use of exogenous testosterone replacement therapy (TRT) has been controversial [1,2]. Traditional, well-supported indications include androgen deficiency in men with hypothalamic, pituitary or testicular pathology to treat low energy, lack of secondary male sexual characteristics, muscle weakness and loss of libido [1-3]. However, the use of TRT in middle aged or older men with low serum testosterone without a pathological basis (hypothalamic, pituitary, or testicular disease) is controversial, with some data supporting TRT use in older males with low testosterone and symptoms to improve lean body mass, bone mineral density, libido and grip strength [2-7]. The safety of TRT has also been a contentious issue with conflicting evidence with regards to its effect on cardiovascular health and the rate of adverse cardiovascular events [2,4,6-12].

Notwithstanding controversies, testosterone prescribing has increased considerably worldwide, with yearly expenditure rising from $150 million in year 2000, to $1.8 billion in 2011 [1,13-17]. In Australia the supply of subsidized testosterone doubled between 2007 and 2011, with most new patients being older than 40 years, and with more General Practitioners than specialists commencing therapy [13]. In response to this, in April 2015 the Pharmaceutical Benefits Scheme (PBS), an Australian Government scheme designed to subsidize the cost of medicines in attempt to allow ready access to medicine required by the Australian public, followed the paths taken by its equivalent bodies in the USA, UK, and Canada and created stricter criteria for the provision of subsidized testosterone replacement [18]. The new criteria establish that all patients must be seen by, referred to, or discussed with a specialist (specialist general paediatrician, specialist paediatric endocrinologist, specialist urologist, specialist endocrinologist, or a Fellow of the Australasian Chapter of Sexual Health Medicine). In patients without established testicular or pituitary disease aged over 40 years the androgen deficiency must not be due to age, obesity, cardiovascular diseases, infertility or drugs, and is defined as two morning blood samples demonstrating testosterone levels <6 nmol/L or testosterone levels between 6 and 15 nmol/L and luteinizing hormone greater than 1.5 times the upper limit of normal or greater than 14 IU/L, whichever is highest [18]. We aimed to examine the effect these changes have had on prescribing patterns in Australia.

MATERIALS AND METHODS

1. Data sources

The PBS represents an Australian publicly funded scheme that subsidizes the cost of medications for eligible patients to improve access. The actual cost of the medicine, also described as the Dispensed Price for Maximum Quantity (DPMQ), is higher than that paid by the patient, of which the maximum payment is $AU40.30 or $AU6.50 for concession card holders (*e.g.*, pensioners). PBS are mostly for outpatient treatment and do not include claims within public hospitals using public hospital funding.

2. Data collection

Pharmaceutical Benefits Schedule Item Reports were queried in May 2019, similar to methodology described previously [19-21]. Annual prescription data from 1992 to 2018, as well as monthly data from April 2014 (one year prior to the PBS changes) to April 2019 were collected for the item numbers listed for TRT, shown in Table 1. Australian Demographic Statistics (according to the Australian Bureau of Statistics) were used to adjust for change in population with time [22].

3. Data analysis

Total and per capita estimates of prescriptions according to individual item, as well as class, were calculated. Population-adjusted data were described per 100,000 men or as a relative index with 2015 taken as the index year (the first year that restrictions were introduced). Cost analysis was performed using the DPMQ and total prescriptions to estimate financial burden due to TRT. Prices obtained in May 2019 were used for costing throughout the study period without indexation. Data analysis and figure generation were performed in Excel (Microsoft, Redmond, WA, USA). Formal statistical hypothesis testing was not performed as this retrospective study sought to illustrate general, longitudinal prescribing patterns.

4. Ethics statement

Institutional ethical board approval or informed consent were not required as the collected data released by

Table 1. Testosterone replacement therapy formulations, according to class and item number, as well as Dispensed Price for Maximum Quantity (DPMQ), brand name, and manufacturer

Class	Item number	Name, form & strength, pack size	Maximum quantity	Repeats	DPMQ	Brand name and manufacturer
Patch	8460G	Testosterone 2.5 mg/24 h patch, 60	1	5	$AU87.78	Androderm® Allergan Australia Pty Ltd.
	8619P	Testosterone 5 mg/24 h patch, 30	1	5	$AU87.78	Androderm® Allergan Australia Pty Ltd.
Gel	8830R	Testosterone 1% (50 mg/5 g) gel, 30×5 g sachets	1	5	$AU87.17	Testogel® Besins Healthcare Australia Pty Ltd.
	10380H	Testosterone 1% (12.5 mg/actuation) gel, 2×60 actuations	1	4	$AU87.17	Testogel® Besins Healthcare Australia Pty Ltd.
Cream/Spray	2341F	Testosterone 2% (30 mg/actuation) solution, 60 actuations	1	5	$AU76.23	Axiron® Eli Lilly Australia Pty Ltd.
	10378F	Testosterone 5% (50 mg/mL) cream, 50 mL	1	6	$AU73.42	Androforte® Lawley Pharmaceuticals Pty Ltd.
Capsule	2115H	Testosterone undecanoate 40 mg capsule, 60	1	5	$AU36.26	Andriol Testocaps® Merck Sharp & Dohme Pty Ltd.
Injection	2114G	Testosterone enanthate 250 mg/mL injection, 3×1 mL syringes	1	3	$AU32.91	Primoteston® Bayer Australia Ltd.
	10205D	Testosterone undecanoate 1 g/4 mL injection, 4 mL vial	1	1	$AU132.33	Reandron® Bayer Australia Ltd.

the Australian Government is publicly available and research did not directly involve human participants.

RESULTS

1. Delivery method

Longitudinal trends in subsidized TRT prescription demonstrated a progressive overall increase since 2000, according to total prescriptions and population-adjusted estimates, with greater use of topical formulations (gel, patch, cream/spray) and injections (Fig. 1A-1D). Capsules were more commonly prescribed than injections until 2004, after which topical formulations (until 2014) then injections (since 2015) have become most commonly subsidized. Since 2015, a 37% decline in total population-adjusted prescriptions was observed (1,399 to 883 per 100,000 persons), mostly due to reduction in use of gels (530 to 338 per 100,000 persons) and creams/sprays (226 to 35 per 100,000 persons). Injections saw an initial increase between 2014 to 2017 (121 to 606 per 100,000 persons), then decline in 2018 (to 445 per 100,000 persons). Specific formulations are outlined in Supplementary Fig. 1. When indexed to 2015 when the restrictions were introduced (Fig. 1E, 1F), all formulations except injections decreased in use.

2. Specific formulations

When considered according to specific formulations, similar trends were observed (Fig. 2). Since comprising approximately 75% of subsidized TRT prescriptions between 1992 and 2000, testosterone undecanoate capsules has decreased to less than 5% (Fig. 2C). A brief period in use of patches peaked in 2004 (31% of prescriptions), after which gels resulted in 70% of prescriptions in 2011, which was maintained with adoption of sprays in 2015. Since 2015, increased use of injections (50%) and 1% gel (30%) comprise the majority of TRT in 2019. Month to month changes for specific formulations between 2011 and 2019 are shown in Supplementary Fig. 2.

3. Cost analysis

A progressive increase in the cost of subsidized TRT was observed between 1992 and 2018. The greatest rate of change was observed from 2013 to 2015, which then slowed after 2015 (Fig. 3). Specifically, TRT costed $AU16,768 per 100,000 persons prior to 2000 (mean cost 1992–2000) to $AU60,895 in 2013 (due to use of gels)

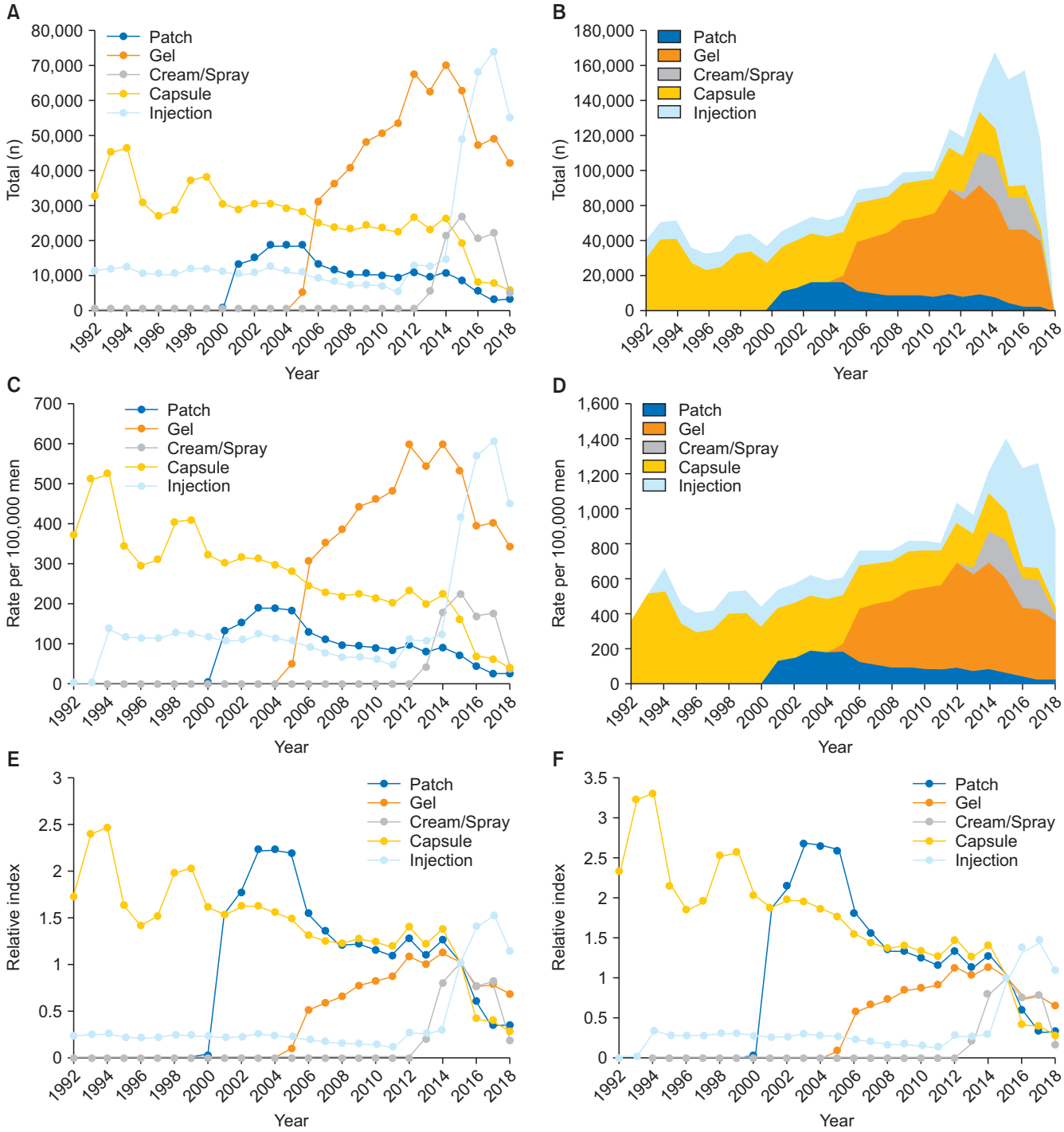

Fig. 1. Subsidized testosterone therapy prescriptions by year from 1992 to 2018 according to class (patch, gel, cream/spray, capsule, injection). (A) Total number of prescriptions. (B) Cumulative analysis of total prescriptions. (C) Prescriptions per 100,000 men. (D) Cumulative analysis of prescriptions per 100,000 men. (E) Total prescriptions relative to 2015 (year when restrictions were introduced). (F) Prescriptions per 100,000 men relative to 2015.

and $AU112,539 in 2018 (due to use of injections). The rate of change in costs slowed after the restrictions were introduced in 2014, costing $AU108,346 in 2015 to $AU112,539 in 2018.

DISCUSSION

The introduction of stricter PBS criteria in April 2015 has halted the growth in subsidized TRT, with a 37% reduction in population adjusted rate of testos-

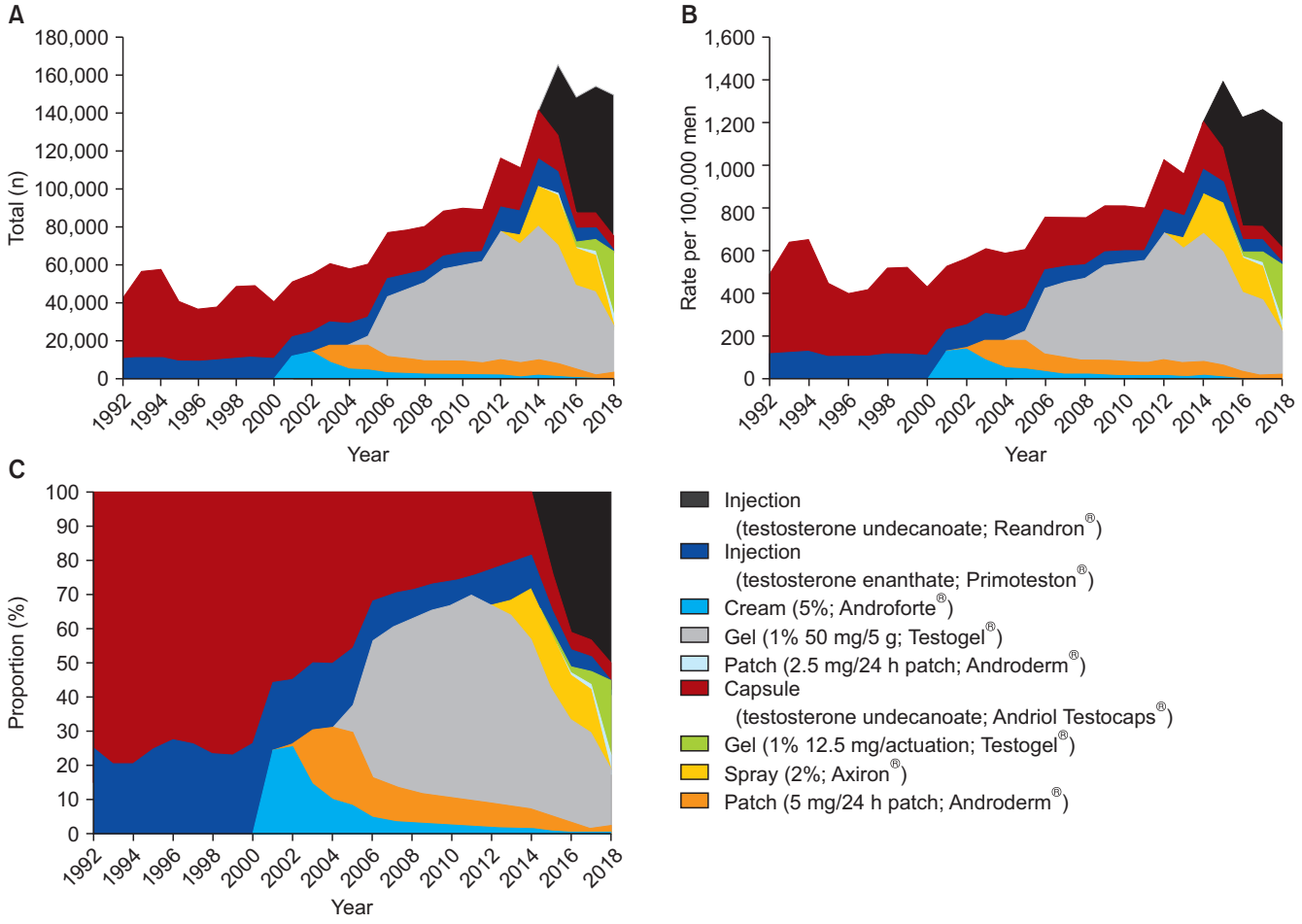

Fig. 2. Subsidized testosterone therapy prescriptions by year from 1992 to 2018 according to specific formulation. (A) Total number of prescriptions. (B) Cumulative analysis of total prescriptions. (C) Proportion of prescriptions over time.

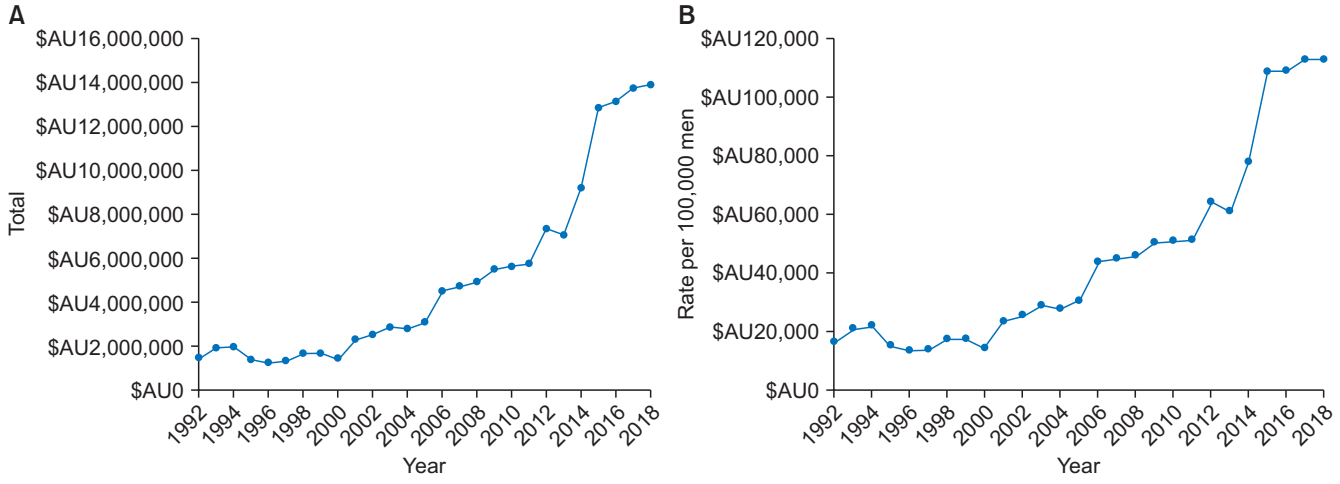

Fig. 3. Financial burden of subsidized testosterone replacement, according to Dispensed Price for Maximum Quantity and total prescriptions. (A) Total cost. (B) Cost per 100,000 men.

terone prescriptions. Prior to such date the population adjusted supply of subsidized testosterone in Australia almost tripled between 2000 and 2015, with the sharpest increase between 2011 and 2015. A previous pharmacoepidemiologic study in Australia had shown that between 1992 and 2010 the inflation adjusted expen-

diture on testosterone replacement increased 4.5 fold based on PBS data and 2.5 fold based on commercial pharmaceutical sales data [23]. Such increase in testosterone prescribing and utilization had also been reported in the USA and Europe by several studies between 2000 and 2011 [24]. However, since 2013 there seems to have been a decrease in testosterone utilization. In the USA separate studies using private health insurance [25] and Veterans Administration data [26] showed decreases in testosterone usage between 2013 and 2016 in the vicinity of 40%, with the sharpest declines coinciding with the releases of article relating testosterone use with cardiovascular disease and a Food and Drug Administration warning about such potential association.

The mode of administration and specific preparations supplied by PBS for testosterone replacement have changed significantly in the analyzed period. Oral testosterone supply has been decreasing from approximately 70% of supplied testosterone in the year 2000 to approximately 5% currently. Between 2000 and 2014 there was an increase in the use of topical testosterone forms (patch, gel, cream). Since its addition to the PBS a long-acting injection agent in 2014 has been increasingly supplied, and in 2018 represented approximately 50% of PBS supplied testosterone. This is consistent with data from the UK [27], and USA, which demonstrated rising use of both topical gel formulations and injections between 2003 and 2013 [28].

The population costs associated with testosterone supply by PBS progressively increased from under $AU20,000 per 100,000 individuals in the year 2000 to more than $AU110,000 in 2018. The sharpest rise was seen after the introduction of a long-acting injection testosterone replacement to PBS. Despite the decrease in supply, costs have not decreased between 2015 and 2018 due to the continuous proportional increase in utilization of such long-acting preparation.

The main limitation of this study is the sole use of the PBS database. Any testosterone prescribed by specialists privately for patients that do not meet the PBS criteria is not captured by this study. Therefore, based on our data it was not possible to fully evaluate the impact of the stricter PBS criteria on overall usage of testosterone in Australia. Also, the available data does not allow for identification of TRT prescribed to women or transgender patients. Moreover we have no data on specific indication and differentiation between new and recurring testosterone usage, patient demographic information, and prescriber characteristics. It is expected that most TRT is being prescribed by either urologists or endocrinologists and that variability in prescribing patterns would occur across specialties.

CONCLUSIONS

This study represents the most comprehensive evaluation of national TRT trends in Australia. The introduction of stricter criteria has decreased the population adjusted supply of PBS subsidized testosterone in Australia. However, such reduction has not lead to decreased costs due to increased supply of long-acting injectable testosterone.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: MW, MJR, EC. Data curation: MW, AM, SR, MJR. Formal analysis: AM, MW, MJR, MP, PET, MW. Writing – original draft: MW, AM, MJR, PET. Writing – review & editing: all authors.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.190166.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/CPRSNJ.

REFERENCES

1. Handelsman DJ. Global trends in testosterone prescribing, 2000-2011: expanding the spectrum of prescription drug misuse. Med J Aust 2013;199:548-51.
2. Morgentaler A. Controversies and advances with testosterone therapy: a 40-year perspective. Urology 2016;89:27-32.
3. Haggan M. Professional: male sexual health: the right balance. AJP 2017;98:46-8, 50.
4. Gruenewald DA, Matsumoto AM. Testosterone supplementa-

tion therapy for older men: potential benefits and risks. J Am Geriatr Soc 2003;51:101-15; discussion 115.
5. Traish AM. Adverse health effects of testosterone deficiency (TD) in men. Steroids 2014;88:106-16.
6. Traish AM. Outcomes of testosterone therapy in men with testosterone deficiency (TD): part II. Steroids 2014;88:117-26.
7. Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, et al.; International Society of Andrology; International Society for the Study of Aging Male; European Association of Urology; European Academy of Andrology; American Society of Andrology. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. Eur Urol 2009;55:121-30.
8. Kelleher S, Conway AJ, Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. J Clin Endocrinol Metab 2004;89:3813-7.
9. Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: from physiology to clinical implications. Eur Urol 2014;65:115-23.
10. Kloner RA. Testosterone replacement therapy: new data on efficacy and cardiovascular safety. J Cardiovasc Pharmacol Ther 2017;22:54-5.
11. Nigro N, Christ-Crain M. Testosterone treatment in the aging male: myth or reality? Swiss Med Wkly 2012;142:w13539.
12. Yeap BB, Grossmann M, McLachlan RI, Handelsman DJ, Wittert GA, Conway AJ, et al. Endocrine Society of Australia position statement on male hypogonadism (part 1): assessment and indications for testosterone therapy. Med J Aust 2016;205:173-8.
13. Pharmaceutical Benefits Scheme. Review of proposed amendments to PBS restrictions for testosterone products [Internet]. Canberra: Australian Government Department of Health; c2014 [cited 2019 May 1]. Available from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2014-07/testosterone-4-1-psd-pbac-07-2014.pdf.
14. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use. Washington, D.C.: U.S. Food and Drug Administration; 2015.
15. Gan EH, Pattman S, H S Pearce S, Quinton R. A UK epidemic of testosterone prescribing, 2001-2010. Clin Endocrinol (Oxf) 2013;79:564-70.
16. Mackee N. Testosterone changes "necessary" [Internet]. Sydney: Medical Journal of Australia; c2015 [cited 2019 May 1]. Available from: https://insightplus.mja.com.au/2015/11/testosterone-changes-necessary/.
17. Perls T, Handelsman DJ. Disease mongering of age-associated declines in testosterone and growth hormone levels. J Am Geriatr Soc 2015;63:809-11.
18. Pharmaceutical Benefits Scheme. Body System [Internet]. Canberra: Australian Government Department of Health; c2017 [cited 2019 May 1]. Available from: http://www.pbs.gov.au/browse/body-system?depth=4&codes=g03ba#g03ba.
19. Perera M, Papa N, Christidis D, McGrath S, Manning T, Roberts M, et al. The impact of the global bacille Calmette-Guérin shortage on treatment patterns: population-based data. BJU Int 2018;121:169-72.
20. Morton A, Williams M, Perera M, Teloken PE, Donato P, Ranasinghe S, et al. Management of benign prostatic hyperplasia in the 21st century: temporal trends in Australian population-based data. BJU Int 2020. doi: 10.1111/bju.15098 [Epub].
21. Services Australia. Pharmaceutical benefits schedule item reports [Internet]. Canberra: Australian Government Department of Health; c2019 [cited 2020 Feb 25]. Available from: http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp.
22. Australian Bureau of Statistics. 3101.0 - Australian Demographic Statistics, Sep 2018 [Internet]. Canberra: Australian Bureau of Statistics; c2019 [cited 2020 Feb 25]. Available from: https://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3101.0Sep%202018?OpenDocument.
23. Handelsman DJ. Pharmacoepidemiology of testosterone prescribing in Australia, 1992-2010. Med J Aust 2012;196:642-5.
24. Anaissie J, DeLay KJ, Wang W, Hatzichristodoulou G, Hellstrom WJ. Testosterone deficiency in adults and corresponding treatment patterns across the globe. Transl Androl Urol 2017;6:183-91.
25. Baillargeon J, Kuo YF, Westra JR, Urban RJ, Goodwin JS. Testosterone prescribing in the United States, 2002-2016. JAMA 2018;320:200-2.
26. Jasuja GK, Bhasin S, Rose AJ. Patterns of testosterone prescription overuse. Curr Opin Endocrinol Diabetes Obes 2017;24:240-5.
27. Layton JB, Li D, Meier CR, Sharpless JL, Stürmer T, Jick SS, et al. Testosterone lab testing and initiation in the United Kingdom and the United States, 2000 to 2011. J Clin Endocrinol Metab 2014;99:835-42.
28. Rao PK, Boulet SL, Mehta A, Hotaling J, Eisenberg ML, Honig SC, et al. Trends in testosterone replacement therapy use from 2003 to 2013 among reproductive-age men in the United States. J Urol 2017;197:1121-6.