

Global trends in testosterone prescribing, 2000–2011: expanding the spectrum of prescription drug misuse

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Since the first report of clinical use of testosterone in 1937,¹ 2 years after its Nobel Prize-winning identification as the male testicular steroid,^{2,3} the sole unequivocal therapeutic indication for testosterone is in replacement therapy for pathological androgen deficiency (AD). This includes disorders of the testis, where damaged Leydig cells cannot produce sufficient testosterone, and of the hypothalamus and/or pituitary, where impaired pituitary luteinising hormone (LH) secretion reduces testosterone production by Leydig cells. Pharmacological androgen therapy — the use of testosterone (or its synthetic androgen analogues) beyond replacement therapy — exploits androgenic effects on muscle, bone, liver or brain in men.⁴ It can also be used to treat various functional AD states where an intact reproductive system responds adaptively to acute or chronic illness (eg, ageing, obesity, diabetes, cardiovascular disease, chronic infections or organ failure syndromes) by reducing testosterone secretion. These uses require high-quality clinical evidence of efficacy, safety and cost-effectiveness from trials featuring randomisation and placebo controls; however, few such trials are available.⁵

Nevertheless, despite the absence of any new approved indications, there have been major and progressive increases in testosterone prescribing in Australia over the past two decades, with striking differences between states, increasing use of costlier newer products and partially effective regulatory curbs on unproven testosterone prescribing.^{6,7} Anecdotally, similar increases have been described in the United States,^{8,9} Switzerland¹⁰ and the United Kingdom,¹¹ but there has been no systematic study of multinational temporal trends in testosterone prescribing.

Abstract

Objective: To provide the first multinational survey of temporal trends in testosterone prescribing, given that anecdotal evidence indicates that it is increasing in some countries, including Australia.

Design: Sales data for all testosterone products were obtained for 41 countries for each year from 2000 to 2011. For each testosterone product type (injectable, implantable, oral, transdermal), units sold were converted into defined monthly doses per year, reflecting total testosterone prescribing per product.

Main outcome measures: National testosterone prescribing rate overall and per product type on a per capita basis.

Results: For every region and 37 of 41 countries, there was a major and progressive increase in defined monthly doses per year per capita over the 11 years surveyed. In most countries, the increases were steeper for the last half of the survey period. The proportion of testosterone prescribing represented by transdermal testosterone products, a surrogate measure of prescribing for older men, increased even more than did the total usage of testosterone products.

Conclusions: In the absence of any new indications, off-label testosterone prescribing has increased in most countries in 2000–2011, especially over the last half of the period. The increased testosterone prescribing appears to be primarily for older men and driven by clinical guidelines that endorse testosterone prescribing for age-related functional androgen deficiency (andropause). By eliminating the fundamental distinction between pathological and functional androgen deficiency, these guidelines tacitly promote increased testosterone prescribing, bypassing the requirement for high-quality clinical evidence of safety and efficacy and creating dramatic increases in prescription of testosterone products.

Methods

Data for sales of all testosterone products for each year from 2000 to 2011 inclusive were obtained from IMS Health for 41 countries. Countries were divided descriptively into six groups: the Anglosphere (Australia, Canada, Ireland, UK, US); Eastern Europe (Bulgaria, Croatia, Czechoslovakia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia); Middle Europe (Austria, Belgium, France, Germany, Luxembourg, the Netherlands, Switzerland); Northern Europe (Denmark, Finland, Norway, Sweden); Southern Europe (Greece, Italy, Spain); and Asia (Hong Kong, China, Japan, Indonesia, Malaysia, the Philippines, Singapore, Thailand, Vietnam). Data were also obtained for Mexico.

Using the World Health Organization definition of standardised dosing (WHO Collaborating Centre for Drug Statistics Methodology, [\[www.whocc.no\]\(http://www.whocc.no\); described in detail elsewhere^{6,7}\) the defined monthly dosage of testosterone was calculated for each product category, country and year. Testosterone products were grouped into four categories as injectable and, using a standard dosage regimen, sales of units were converted into monthly dose equivalents. For each country and region, total testosterone units were calculated for each product category per year. These total use estimates were adjusted to a population basis using annual national population estimates obtained from the US Census Bureau based on annual estimates for national population. This method uses commercial \(wholesale\) sales of testosterone products as a surrogate for testosterone prescribing and assumes \(i\) a constant proportion of adult males in each country's population over time and between countries, and \(ii\) a steady state existing between pur-](http://</p>
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1 Testosterone use, 2000–2011, by country or region

Country/region	Defined monthly doses (% transdermal)*											
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Australia	9.6 (1%)	11.5 (10%)	12.5 (13%)	12.2 (13%)	12.2 (12%)	13.1 (13%)	13.1 (23%)	13.6 (23%)	15.1 (22%)	16.5 (22%)	17.4 (22%)	17.9 (23%)
Canada	10.0 (0)	11.3 (3%)	40.4 (7%)	82.1 (86%)	102.3 (89%)	108.5 (90%)	115.4 (91%)	122.3 (91%)	135.7 (91%)	220.0 (95%)	333.5 (96%)	385.5 (97%)
Ireland	1.2 (45%)	1.9 (41%)	1.7 (4%)	1.6 (54%)	1.9 (67%)	2.3 (72%)	2.5 (72%)	2.9 (74%)	3.6 (69%)	4.6 (64%)	5.0 (60%)	5.4 (58%)
United Kingdom	3.9 (15%)	4.1 (16%)	3.3 (21%)	3.6 (24%)	3.8 (37%)	4.2 (43%)	4.6 (45%)	5.4 (49%)	6.2 (51%)	7.9 (47%)	8.9 (48%)	9.8 (50%)
United States	10.3 (31%)	15.3 (53%)	19.4 (67%)	19.0 (61%)	19.3 (57%)	24.2 (66%)	26.0 (67%)	32.6 (71%)	39.7 (72%)	46.5 (69%)	52.9 (68%)	98.5 (78%)
Mexico	3.7 (0)	3.0 (0)	2.4 (0)	2.0 (0)	1.6 (0)	1.5 (0)	1.6 (0)	1.7 (2%)	1.9 (6%)	2.3 (7%)	2.0 (8%)	1.9 (11%)
Eastern Europe†	1.9 (0)	1.6 (0)	1.8 (0)	1.3 (0)	1.4 (0)	1.4 (1%)	1.7 (4%)	1.6 (6%)	1.8 (7%)	2.0 (9%)	1.8 (9%)	2.7 (7%)
Middle Europe‡	4.3 (7%)	4.8 (6%)	5.1 (6%)	5.0 (17%)	4.3 (27%)	4.8 (23%)	5.5 (24%)	6.0 (26%)	6.5 (27%)	7.1 (28%)	7.8 (29%)	8.5 (28%)
Northern Europe‡	4.5 (14%)	4.8 (14%)	5.1 (14%)	5.2 (14%)	5.5 (26%)	6.4 (32%)	10.5 (47%)	12.6 (52%)	14.8 (56%)	16.6 (57%)	19.3 (60%)	22.1 (62%)
Denmark	1.6 (7%)	1.7 (3%)	1.7 (0)	1.8 (0)	2.0 (7%)	2.6 (9%)	4.9 (9%)	5.2 (10%)	5.4 (13%)	5.8 (15%)	6.3 (20%)	6.9 (21%)
Finland	5.4 (9%)	5.5 (7%)	6.0 (7%)	6.3 (10%)	6.8 (24%)	7.9 (28%)	9.2 (28%)	10.1 (29%)	11.6 (31%)	13.5 (31%)	14.4 (32%)	15.1 (34%)
Norway	5.1 (10%)	5.6 (9%)	6.1 (10%)	5.9 (10%)	6.7 (20%)	6.9 (24%)	8.3 (2%)	9.1 (23%)	9.5 (23%)	10.6 (23%)	11.5 (24%)	12.6 (25%)
Sweden	5.5 (20%)	5.8 (21%)	6.0 (22%)	6.2 (21%)	6.3 (34%)	7.5 (44%)	15.8 (67%)	20.4 (72%)	25.0 (75%)	28.2 (76%)	34.1 (77%)	40.2 (78%)
Southern Europe‡	5.6 (2%)	5.5 (6%)	5.3 (6%)	4.7 (7%)	4.5 (11%)	4.7 (15%)	5.1 (15%)	5.8 (17%)	6.3 (19%)	6.7 (21%)	6.9 (21%)	7.2 (21%)
Asia**	0.4 (0)	0.4 (0)	0.4 (0)	0.3 (0)	0.3 (0)	0.3 (0)	0.3 (0)	0.3 (0)	0.4 (0)	0.4 (0)	0.4 (0)	0.5 (0)

* Per year per 1000 population; proportion given via transdermal products (gel, patch). † Bulgaria, Croatia, Czechoslovakia, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia. ‡ Austria, Belgium, France, Germany, Luxembourg, the Netherlands, Switzerland. § Denmark, Finland, Norway, Sweden. ¶ Greece, Italy, Spain. ** China (hospitals), Hong Kong, Indonesia, Japan, Malaysia, the Philippines, Singapore, Thailand, Vietnam. ◆

chase, prescribing and clinical use of testosterone products according to their approved regimens.

Results

Over 11 years, total testosterone sales increased 12-fold globally, rising from \$150 million in 2000 to \$1.8 billion in 2011. For all regions and 37 of 41 countries, there was a progressive and increasingly steep increase in per capita use over that period (Box 1). This rise was markedly steeper from the middle of the decade, consistently in almost all countries (Box 2). In parallel, the proportion of testosterone sales as transdermal products also increased overall as well as in each region, especially in the second half of the decade for most countries (Box 1).

Discussion

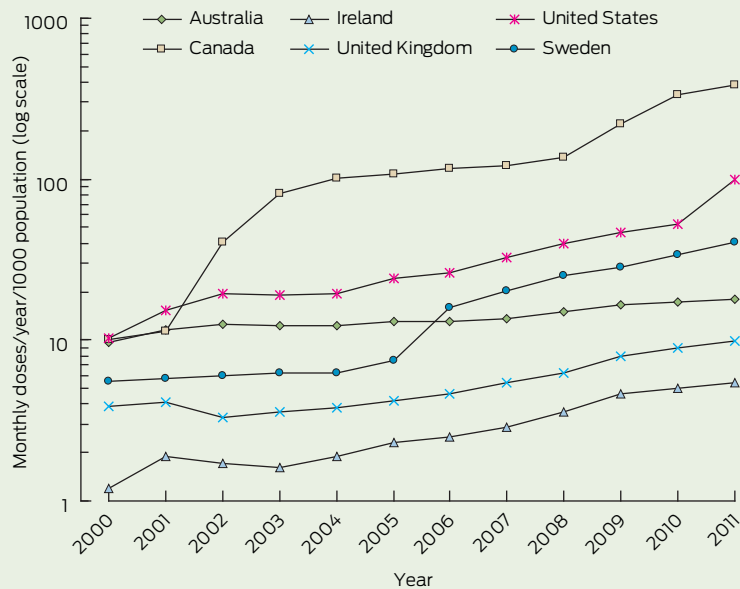
This study shows a large and progressive increase in testosterone prescrib-

ing across a wide range of countries over more than a decade. This is not due to any new indications for testosterone, and the rising trend accelerated over the last half decade of the survey period. The most dramatic increases in per capita testosterone prescribing were observed in Canada, which displayed an almost fourfold higher rate than the next country, its southern neighbour the US (however, a similar pattern did not occur between the US and its southern neighbour Mexico). This increase is most probably due to internet pharmacies physically based in Canada, which appear not to be subject to national prohibitions of import and export controls of androgens as restricted drugs and are beyond the US Food and Drug Administration's regulatory reach. In contrast, other national data are likely to reflect use only within a country. These findings closely resemble, and widen, the spectrum of prescription drug misuse, which has been described as a mod-

ern epidemic¹² involving the misuse of psychoactive drugs such as opioids, sedatives and stimulants, as well as non-psychoactive drugs such as antibiotics.^{13,14} Notably, testosterone has long been known to have mood-elevating effects,¹⁵ reflected in its modest efficacy as an adjuvant antidepressant,^{16,17} and hypomania as an overdosage side effect.¹⁸

Testosterone prescribing was already increasing before 2000 when this survey commenced.^{6,8} The reasons for this coordinated global increase in testosterone prescribing are speculative. The dramatic differences between even neighbouring countries is an indication that differences in local or regional marketing are responsible as shown previously for Australian states.^{6,8} The impact of direct-to-consumer advertising in the US, materially unchanged during the period of survey, would be largely confined to North America. More likely, a major contributor, especially in the second half of the decade,

2 Increasing testosterone use, 2000–2011, in selected countries



appears to be the permissive US¹⁹ and European-based²⁰ guidelines for testosterone prescribing, first published in 2005–2006 and republished virtually unchanged 4 years later.^{21,22} The European-based guidelines appeared in seven different peer-reviewed journals, and both guidelines have been frequently cited (> 1300 times; Thomson Reuters Web of Knowledge, 20 June 2013, <http://wok.mimas.ac.uk/news/2013/20130620.html>). These guidelines are widely understood to define and endorse testosterone prescription for age-related functional AD (also known as andropause or late-onset hypogonadism).²³ In eliminating the distinction between pathological and functional AD, these guidelines promote unproven off-label testosterone prescribing, particularly for older men, bypassing the need for high-quality evidence from randomised placebo-controlled clinical trials.⁵

The rising proportion of transdermal products may reflect that the increased testosterone prescribing was primarily for older men, although the age and indications for treatment were not available for this analysis. Daily-use testosterone products are a convenient surrogate metric for testosterone prescribing for older men, as short-acting products allow for rapid cessation with a new diagnosis of prostate cancer. In contrast, younger

men, facing a lifetime of treatment, prefer long-acting injections, which facilitate the continuity and convenience of long-term treatment.²⁴

The known prevalence of pathological AD (about 0.5% of men²⁴) equates to about 15 defined monthly doses per year per 1000 population. Population-linkage registry data from the UK²⁵ and Denmark²⁶ indicate severe underdiagnosis of Klinefelter syndrome (KS), the most frequent cause of pathological AD. Nevertheless, it is highly unlikely that recent steep increases in testosterone prescribing can be attributed to rectifying underdiagnosis of KS. Not only does total testosterone prescribing in some countries exceed the maximum amount that could be attributed to pathological AD, there is no evidence that the diagnosis of KS has increased in recent years.^{6,27} In contrast, the estimated population prevalence of age-related functional AD among older men is up to 40%,²⁸ more usually 10%–25%,^{29–31} with even the lowest estimates of 2%–3%³² representing major (five- to 100-fold) increases in potential market size over pathological AD.

The potential harm of testosterone overuse in older men is highlighted by adverse cardiovascular effects of testosterone in frail, older men.³³ Nevertheless, previous longer and higher dose studies produced no similar

excess cardiovascular harms,³⁴ although the bias in underreporting of cardiovascular harm in industry-sponsored studies may lead to underestimating the risk.³⁵ Such testosterone-induced cardiovascular harm predicts that the substantial increases in testosterone prescribing for older men may lead to increased incidence of cardiovascular disease among older men, warranting ongoing population-level surveillance. In the interim, testosterone prescribing for functional AD, notably among older men without pathological hypogonadism, should be confined to well controlled and adequately powered clinical trials that aim to determine the efficacy and safety of testosterone prescribing for andropause.

Limitations of this study include that no information on patient age or the indications for prescribing was available. However, it is most likely that the increased prescribing was for older men with functional AD. The study also did not include testosterone sold by compounding pharmacies. Androgens (including testosterone) obtained illicitly via the internet or other non-medical sources are at least partly included, to the extent that virtually all testosterone originates from commercial production facilities that supply wholesalers.

This study provides the first multinational view of testosterone prescribing. It shows coordinated, global increases in off-label testosterone prescribing, apparently mainly for older men, driven by permissive guidelines promoting evidence-free prescribing for functional AD including andropause. This overuse of testosterone shares many features of, and expands the spectrum of, prescription drug misuse.

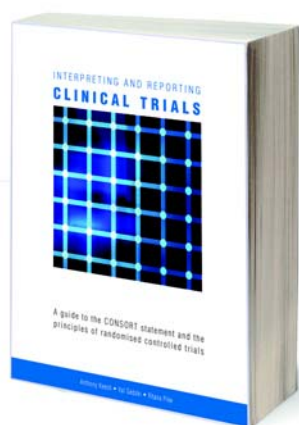
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