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Trends in Testosterone Replacement Therapy Use from 2003 to 2013 among Reproductive-Age Men in the United States

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Abstract

Purpose: Although testosterone replacement therapy use in the United States has increased dramatically in the last decade, to our knowledge trends in testosterone replacement therapy use among reproductive-age men have not been investigated. We assessed changes in testosterone replacement therapy use and practice patterns among 18 to 45-year-old American men from 2003 to 2013 and compared them to older men.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Materials and Methods: This is a retrospective, cross-sectional analysis of men 18 to 45 and 56 to 64 years old who were enrolled in the Truven Health MarketScan® Commercial Claims Databases throughout each given calendar year from 2003 to 2013, including 5,094,868 men in 2013. Trends in the yearly rates of testosterone replacement therapy use were calculated using Poisson regression. Among testosterone replacement therapy users, the Cochran-Armitage test was used to assess temporal trends in age, formulation type, semen analysis and serum testosterone level testing during the 12 months preceding the documented use of testosterone replacement therapy.

Results: Between 2003 and 2013, there was a fourfold increase in the rate of testosterone use among 18 to 45-year-old men from 29.2/10,000 person-years to 118.1/10,000 person-years ($p < 0.0001$). Among testosterone replacement therapy users, topical gel formulations were initially most used. Injection use then doubled between 2009 and 2012 (23.5% and 46.2%, respectively) and surpassed topical gel use in 2013. In men 56 to 64 years old there was a statistically significant threefold increase in testosterone replacement therapy use ($p < 0.0001$), which was significantly smaller than the fourfold increase in younger men ($p < 0.0001$).

Conclusions: In 2003 to 2013, testosterone replacement therapy use increased fourfold in men 18 to 45 years old compared to threefold in older men. This younger age group should be a focus for future studies due to effects on fertility and unknown long-term sequelae.

Keywords

testis; testosterone; hypogonadism; infertility; male; age groups

Testosterone replacement therapy use in the United States has increased dramatically during the last decade, emerging as one of the fastest growing pharmaceutical products.[1–4] During the same period, terms such as “low T” and “andro-pause” have become household names for a syndrome characterized by symptoms of fatigue, mood changes, muscle and fat redistribution, and problems with sexual function.[5] The understanding of TRT related effects has lagged behind the rapid increase in use of these medications.

Currently, the risks and benefits of TRT in patients of different ages with different comorbidities are poorly understood.[6] Although low testosterone has been associated with diabetes, metabolic syndrome, vascular events and increased mortality, studies have yielded inconsistent findings.[7–9] Further, few studies have demonstrated the ability of TRT to reverse many of these conditions[10,11] and some have suggested an increased risk of vascular complications among TRT users.[12–14] Accordingly, FDA has not recommended TRT for vague symptoms such as fatigue.[15]

Although most studies of trends in TRT use have focused on elderly patients,[12,13] less is known about use by younger men. However, reproductive-age men are certainly at risk for undesired adverse effects on fertility and this group should be examined. Exogenous testosterone causes negative feedback on the hypothalamic-pituitary-gonadal axis, thereby suppressing pituitary gonadotropins and resulting in a decrease in endogenous testosterone production, intratesticular testosterone levels and sperm production. Beyond the fertility

concerns, younger patients are likely at risk for long-term use and increased cumulative exposure to TRT, along with any poorly understood effects of such exposure.

Despite these concerns, to our knowledge trends in TRT use in younger men have not been specifically studied to date. We examined trends in outpatient pharmaceutical claims for testosterone and related practice patterns among reproductive-age men (18 to 45 years old) in the United States.

MATERIALS AND METHODS

Data were derived from the 2003 to 2013 Truven Health MarketScan Commercial Claims Databases, which is a publicly available product including de-identified health insurance claims of individuals with coverage by select employer sponsored health insurance plans. Our analysis included United States outpatient pharmaceutical and service claims for men 18 to 45 years old who were continuously enrolled (more than 11 months) during a given calendar year. Although testosterone use among reproductive-age men was the focus of the study, the older cohort of males (ages 56 to 64 years) was examined to compare the changing rate of TRT use in older men to that in younger men. For each year, we used NDC (National Drug Code) to identify filled outpatient drug claims for testosterone, including intramuscular injection, transdermal patch, topical gel and implantable pellet formulations. Implantable pellets were also identified using the CPT code for subcutaneous pellet implant (11980).

We calculated the annual rates of testosterone use per 10,000 person-years for the younger and older groups. We used Poisson regression to test for trends in use during 2003 to 2013 and assess for a difference in the magnitude of increased use between the younger and older age groups. Among men 18 to 45 years old with 1 or more filled testosterone prescription, we calculated the annual distributions of age, formulation, proportion with multiple filled prescriptions and proportion with filled prescriptions for more than 1 formulation type.

We also calculated the percent of 18 to 45-year-old men on TRT with an insurance claim for semen analysis or serum testosterone laboratory testing within 1 year prior to the date of the first filled prescription in a given calendar year. To reduce misclassification of patients who had recently joined insurance plans tracked by MarketScan and who might have undergone previous testing elsewhere, we repeated this analysis requiring 2 years of continuous enrollment for inclusion in this analysis. The Cochran-Armitage test was used to assess temporal trends in semen analysis and testosterone testing.

Two-tailed $p < 0.05$ was considered statistically significant. SAS®, version 9.3 was used for all analyses. Cells with counts less than 30 were suppressed to maintain reliability. MarketScan is a publicly available database that does not contain direct personal identifiers. Thus, review by the CDC (Centers for Disease Control and Prevention) institutional review board was not required.

RESULTS

Between 2003 and 2013, the annual population of continuously enrolled 18 to 45-year-old men increased from 2,077,035 to 5,094,868 (table 1). Over this 11-year period, there was a fourfold increase in the rate of testosterone use among these men from 29.2/10,000 (6,066 users) to 118.1/10,000 person-years (60,194 users) ($p < 0.0001$, see figure). Among testosterone users 18 to 45 years old, the use of topical gel formulations was most common in 2003 at 66.8% but it decreased to 44.6% by 2013 (table 2). The proportion of patients on TRT using injections increased marginally between 2003 and 2009 from 20.7% to 23.5% but it then doubled to 56.1% by 2013. From 2003 to 2013, the proportion using transdermal patches decreased from 22.3% to 4.2%, while implantable pellet use rose from less than 1% to 3.9%.

During this period, the number of 55 to 64-year-old men included in the database increased from 660,407 to 1,690,417. Among these men, the rate of testosterone use increased threefold from 125.2/10,000 person-years (8,269 users) in 2003 to 374.3/10,000 person-years (63,277 users) in 2013 ($p < 0.0001$). This threefold increase was significantly smaller than the fourfold increase seen in younger men ($p < 0.0001$).

In all years, 75% of users among reproductive-age men were between 35 and 45 years old (table 2). Around 75% of reproductive-age men who used TRT filled more than 1 prescription, with a higher proportion refilling prescriptions in more recent years. Between 6% and 10% of reproductive-age men filled prescriptions for more than 1 formulation of TRT in each year.

Approximately a third of reproductive-age men who used TRT in 2003 had a testosterone level checked within 1 year before filling TRT prescriptions compared to nearly 80% of men by 2013 ($p < 0.001$). During the study period, less than 2% of these men had undergone a semen analysis as documented by an insurance claim within a year prior to using testosterone (table 2).

DISCUSSION

To our knowledge, this is the first study to examine trends of TRT use in reproductive-age men. We found a fourfold increase in TRT use in men 18 to 45 years old between 2003 and 2013, which was even greater than the threefold increase seen in the older group. There was also a remarkable shift in formulation choice toward intramuscular injection therapy during this time. Although the proportion of men on TRT who had serum testosterone levels checked has increased, a large fraction of men might be receiving treatment without first assessing baseline testosterone levels or without appropriate monitoring while on treatment.

Although studies of adverse events associated with TRT use have generally been short term and done in elderly patients, possible adverse effects have included an increased risk of cardiovascular disease and mortality.[12–14] This is particularly concerning for younger men who might be exposed over many decades, unlike men who start TRT later in life. In fact, we found a modest but significant upward trend in the fraction of reproductive-age men who used TRT and filled more than 1 prescription, which suggests more men are staying

on TRT beyond a short trial period. Although the risks and benefits of TRT are poorly understood and controversial, the potential for unknown risks of long-term exposure should be considered.

One well documented effect of exogenous testosterone is the suppression of male fertility.[16] However, patients and providers are not always aware of the effect of TRT on native testicular function.[17] A 2012 survey of urologists showed that 25% of respondents indicated that they would treat infertile males with testosterone while the patient actively pursued conception.[18] Similarly, studies suggest that a substantial proportion of patients present for fertility evaluation while actively using TRT. A recent study found that 7% of men seeking infertility evaluation were using exogenous testosterone at the time of presentation.[16] Notably, more than 20% of these men failed to recover spermatogenesis after stopping TRT, although preexisting causes of spermatogenic dysfunction (including genetic or karyotype abnormalities, prior infections or prior chemotherapy exposure) could also be to blame.

Exogenous testosterone must be seen as having contraceptive effects and patients in the reproductive years need to be aware of this negative effect. There are medications (including synthetic gonadotropins, selective estrogen receptor modulators and aromatase inhibitors) that can raise serum and intratesticular testosterone levels, and preserve spermatogenesis. Although none of these medications are FDA approved for the treatment of male hypogonadism or male infertility, they are frequently used off label by male infertility specialists. In addition, these medications can have unintended effects, including a paradoxical decrease in semen quality and complications related to changes in estrogen levels.

In the CDC NSFG (National Survey of Family Growth) for 2006 to 2010, 52% of men fathered the first child between ages 18 and 30 years, and another 24% fathered the first child between ages 30 and 40 years.[19] Thus, fertility is still important to men in the fourth decade of life. However, many men around age 40 years use TRT,[1] putting them at risk for unwanted effects on fertility. The published study that included the youngest patients to date showed that men 40 to 49 years old had the highest increase in TRT use of all age groups (a 4.24-fold increase between 2001 and 2011).[1] However, men in the peak reproductive years (ie younger than 40 years) were not studied.

Broadening indications for treatment as perceived by physicians and patients may be contributing to the rapid growth of TRT.[4] Although the FDA recently reasserted its position on the limited indications for TRT,[20] North American and European medical society practice guidelines have effectively expanded the indications for treatment through fairly permissive definitions of hypogonadism.[6,21] In general, they suggest that men can be treated in the presence of symptoms and low or borderline serum testosterone levels. However, the AUA (American Urological Association) Position Statement on Testosterone Therapy specifically states that many “symptoms [of testosterone deficiency] are nonspecific and may be multifactorial in origin...[and] may not be necessarily linked to hypogonadism alone.”[22] These symptoms can be incidental, due to other causes or part of the natural process of aging.

There are also concerns about an increased number of filled TRT prescriptions in the absence of documented low testosterone levels.[1–3,23] FDA estimated that only 25% of TRT users have baseline testosterone levels checked.[15] Our findings support these concerns. On our initial analysis, only a third of reproductive-age men using TRT in 2003 had a testosterone level checked in the 12 months preceding TRT use. Although more than 75% of men were being checked by 2012 ($p < 0.0001$), the remainder of these men on TRT might not have had a documented baseline testosterone level. The increase in testosterone level checks likely reflects advertising that encourages men to routinely have testosterone levels checked and multiple TRT guidelines released during this period that highlighted the importance of checking a testosterone level before starting TRT.[6,21,22] We repeated our analysis using a 2-year minimal continuous enrollment to ensure that we were not improperly classifying patients who had a testosterone level checked outside the MarketScan population before transferring to care in the system. This revealed a slightly increased rate of testosterone level checks, that is up to 79.7% in 2013 (table 2).

Another large factor in patient and physician education and practice is DTCPA, which is now the most prominent source of health information reaching the general public.[24] DTCPA campaigns are unsolicited efforts by pharmaceutical companies to disperse information about medicine products to the general public.[24] They are thought to have both positive and negative influences on public health.[25] DTCPA marketing expenditures for TRT have rapidly increased in recent years and they have paralleled increases in TRT use.[26–28] Moreover, although the Endocrine Society recommends against routine screening for low testosterone,[6] TRT manufacturers have disseminated nonvalidated questionnaires for patients to screen themselves for possible hypogonadism. In addition, others have pushed for screening in asymptomatic men by grouping testosterone level testing with routine screening tests such as serum glucose and lipid levels.[29] Finally, pharmaceutical company presence and event sponsorship at medical conferences might also be affecting physician prescribing practices.

Our analysis also demonstrated changing practice patterns with regard to formulation types. In 2008, topical gels accounted for 75% of TRT use compared to 22% for injections but in 2009 there was a rapid change toward injection therapy. By 2013, more than half of all TRT users were prescribed injection formulations. One possible explanation for the shift involves the release of a May 2009 FDA statement requiring box label changes regarding topical gels and secondary exposure to women and children.[30] Another potential reason for the shift to injection therapy could be cost as some insurance companies started to limit the availability and choices of expensive topical gel formulations. Finally, men might be turning away from topical gels due to the inconvenience of daily application but this would not explain the timing or the magnitude of this shift.

We found that less than 1.5% of men on TRT underwent a semen analysis within 1 year prior to starting medication. However, this value could be artificially low since semen analyses are often performed at fertility centers and may not be covered by insurance and/or captured by MarketScan. In addition, the finding is difficult to interpret since other indications for semen testing exist (eg infertility or vasectomy). Of note, if a patient is not concerned about fertility effects, there is no specific indication for semen analysis before or

after starting TRT. Further, men might refuse to do a semen test if it is not covered by their insurance plan.

Our study has several limitations pertaining to the use of MarketScan data, primarily in the generalizability of our findings. The MarketScan database includes health insurance claims for individuals with coverage by select employer sponsored health insurance plans. Thus, the included patients may not be representative of all American men. The data are generated from fully paid and adjudicated claims, and include complete outpatient prescription information, including mail order prescriptions and specialty pharmacies. Thus, nearly all testosterone claims should be captured since they are typically covered by insurance.

Although prescription drug information and laboratory testing data in MarketScan are thought to be fairly comprehensive, laboratory test results such as testosterone levels were not available. In addition, we could not assess the medical specialties of prescribing physicians. While MarketScan data may be subject to inaccuracies associated with claims data, validity checks are done for select fields, including diagnosis and procedure codes, gender and age, whereby reported data are compared with lists of possible valid values for those fields. Reasonableness checks are also used, which compare the relationship between 2 or more fields (eg diagnosis against gender) to ensure that the data are consistent with expected values. Invalid information is corrected or set to missing.

CONCLUSIONS

TRT use by reproductive-age men represents a large proportion of the growing testosterone market. The rate of TRT use in this age group has increased rapidly and even more so than in older men. A substantial fraction of TRT users might be receiving treatment without proper indications for treatment, including documentation of a low serum testosterone level. Because investigations of the safety and efficacy of TRT have focused on short-term outcomes in elderly patients, future studies should include or focus on long-term safety and efficacy outcomes with testosterone treatment among men of all ages, and the impact on fertility among younger patients should be highlighted. The negative effects of exogenous testosterone on spermatogenesis must be part of the public awareness of TRT.

DTCPA, government agency (FDA) announcements and professional society guidelines might heavily influence TRT related practice patterns.[5] As our understanding of the positive and negative effects of TRT become clearer, these avenues of communication could be useful tools to ensure safe and informed use of the medications and minimize undesired side effects and complications.

Abbreviations and Acronyms

DTCPA	direct to consumer pharmaceutical advertising
FDA	Food and Drug Administration
TRT	testosterone replacement therapy

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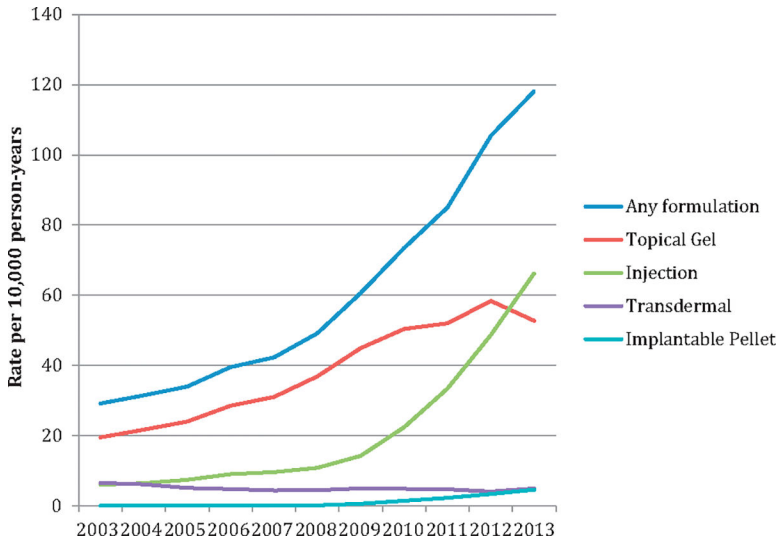

Overall and formulation specific rates of TRT use in American men 18 to 45 years old in 2003 to 2013.

Table 1.

Yearly totals of patients, and overall and formulation specific rate of testosterone replacement therapy in American men 18 to 45 years old in 2003 to 2013

		Rate/10,000 person-yrs*				
Yr	**Total Population**	**Any ormulation**	**Topical Gel**	**Injection**	**Transdermal Patch**	**Implantable Pellet**
2003	2,077,035	29.2	19.5	6.1	6.5	—
2004	2,071,783	31.5	21.7	6.5	6.1	—
2005	2,026,352	34.0	24.1	7.4	5.1	—
2006	1,940,942	39.6	28.6	9.0	4.8	—
2007	2,855,018	42.3	31.1	9.6	4.4	0.2
2008	3,903,149	49.2	36.9	10.9	4.5	0.2
2009	4,550,784	60.6	44.9	14.3	5.0	0.6
2010	4,890,433	73.5	50.4	22.5	4.9	1.4
2011	5,727,194	85.0	52.0	33.4	4.7	2.3
2012	5,978,073	105.5	58.3	48.7	4.1	3.4
2013	5,094,868	118.1	52.7	66.3	5.0	4.6

*Cell was suppressed if the value was less than 30.

Table 2.

Trends in characteristics of men with at least 1 filled testosterone prescription and testosterone replacement therapy users who underwent testosterone or semen analysis testing within 1 year of filling testosterone replacement therapy prescription analyzed by 2-year continuous enrollment inclusion criterion

	% 2003	% 2004	% 2005	% 2006	% 2007	% 2008	% 2009	% 2010	% 2011	% 2012	% 2013
At least 1 testosterone prescription											
No. pts	6,066	6,526	6,896	7,677	12,067	19,202	27,590	35,936	48,665	63,044	60,194
Age:											
18–24	3.9	3.9	3.6	3.2	3.2	3.1	3.1	2.9	2.9	2.8	2.6
25–34	18.4	17.7	18.3	17.5	17.7	18.3	18.5	17.7	17.9	17.8	17.1
35–45	77.7	78.4	78.1	79.2	79.1	78.6	78.5	79.4	79.2	79.5	80.2
More than 1 filled TRT prescription	73.4	73.8	73.1	73.1	73.0	73.2	73.7	73.8	73.8	75.1	75.8
Formulation:											
Transdermal patch	22.3	19.5	15.0	12.1	10.5	9.1	8.3	6.6	5.5	3.9	4.2
Injection	20.7	20.6	21.9	22.8	22.8	22.1	23.5	30.6	39.3	46.2	56.1
Topical gel	66.8	69.0	70.7	72.2	73.5	75.0	74.1	68.6	61.2	55.3	44.6
Implantable pellet	—	—	—	—	0.4	0.4	1.0	2.0	2.7	3.2	3.9
More than 1 type *	9.7	9.1	7.7	7.2	7.0	6.5	6.7	7.5	8.5	8.4	8.5
Testosterone or semen analysis											
No. pts	2,853	4,694	5,166	5,056	6,421	11,235	17,945	23,266	33,029	47,399	41,796
Semen	—	1.8	1.7	1.6	1.3	1.7	1.7	1.5	1.4	1.4	1.2
Testosterone	33.2	57.9	60.1	64.4	68.8	72.7	75.8	75.6	76.4	79.3	79.7

Cell was suppressed if value was less than 30 and all Cochran-Armitage p <0.001.

* Filled prescriptions for combination of transdermal patch, topical gel and/or injection.