

Testosterone Lab Testing and Initiation in the United Kingdom and the United States, 2000 to 2011

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Context: New formulations, increased marketing, and wider recognition of declining testosterone levels in older age may have contributed to wider testosterone testing and supplementation in many countries.

Objective: Our objective was to describe testosterone testing and testosterone treatment in men in the United Kingdom and United States.

Design: This was a retrospective incident user cohort.

Setting: We evaluated commercial and Medicare insurance claims from the United States and general practitioner healthcare records from the United Kingdom for the years 2000 through 2011.

Participants: We identified 410 019 US men and 6858 UK men who initiated a testosterone formulation as well as 1 114 329 US men and 66 140 UK men with a new testosterone laboratory measurement.

Main Outcome Measures: Outcome measures included initiation of any injected testosterone, implanted testosterone pellets, or prescribed transdermal or oral testosterone formulation.

Results: Testosterone testing and supplementation have increased pronouncedly in the United States. Increased testing in the United Kingdom has identified more men with low levels, yet US testing has increased among men with normal levels. Men in the United States tend to initiate at normal levels more often than in the United Kingdom, and many men initiate testosterone without recent testing. Gels have become the most common initial treatment in both countries.

Conclusions: Testosterone testing and use has increased over the past decade, particularly in the United States, with dramatic shifts from injections to gels. Substantial use is seen in men without recent testing and in US men with normal levels. Given widening use despite safety and efficacy questions, prescribers must consider the medical necessity of testosterone before initiation. (*J Clin Endocrinol Metab* 99: 835–842, 2014)

Exogenous testosterone has long been the standard treatment in men with hypogonadism, a condition resulting in low testosterone levels. Classical hypogonadism results from a disturbance of the pituitary-hypothalamic-gonadal axis, leading to disrupted testosterone production and a syndrome of loss of muscle mass and body

hair, low libido, fatigue, and other less specific signs and symptoms (1). However, testosterone levels gradually decrease with increasing age (2–6) and in the presence of chronic diseases (4, 5, 7, 8), obesity (4, 5, 7), and smoking (5). As western populations age and the obesity/diabetes epidemic continues, there may be an increasing number of

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Abbreviations: CPRD, Clinical Practice Research Datalink; CPT, Current Procedure Terminology; PY, person-years.

older men with lower testosterone levels (6) without fully meeting diagnostic or symptomatic criteria for hypogonadism (9). Considerable controversy exists as to the necessity, utility, and safety of widespread testosterone treatment in these men (10–14).

Current clinical guidelines recommend that testosterone supplementation be initiated in patients with symptomatic, unequivocally low testosterone levels confirmed by repeated laboratory tests (1), and guidelines discourage routine treatment of older men based on one low testosterone measurement (1, 9). However, the recognition of individuals with age-related reduced testosterone is increasing, and recent reports suggest increased testosterone use in the United Kingdom (15), the United States (16), and other countries around the world (17, 18).

There is considerable disagreement over the definition of testosterone deficiency, which has led to a lack of consensus over when to initiate testosterone therapy (1, 9, 19). Discrepancies exist regarding the lower bound of a normal testosterone range (20) (estimates range from 200–350 ng/dL), which can lead to inconsistent interpretation of testosterone measurements between physicians and testing facilities. Additionally, there is wide variation in assay results between laboratories (21, 22) complicating identification of clinically meaningful reduced testosterone levels when applying common reference ranges to results from different testing facilities. There is not an agreed upon, standard population in whom normal levels have been established; many testosterone assay reference ranges have been determined in populations of healthy, younger men, which may not be generalizable to older men who may experience normal, natural declines throughout older age and chronic diseases. And lastly, the level of testosterone deficiency at which adverse muscle symptoms manifest seems to vary widely among individuals (23), further obscuring the meaning of a single low or normal test result. The patterns of testosterone initiation relative to baseline testing need to be described to understand the larger use of testosterone in the general population and identify use in potentially nonindicated men.

Vast differences in medication use between the United Kingdom and United States have been observed in various medication classes (24–27), and heavy direct-to-consumer marketing in the United States may further differentially increase testosterone use in the United States. In light of unsettled potential safety concerns (28–31), it is important to assess and describe the distribution of testosterone use. We describe and compare the patterns of testosterone testing and initiation of testosterone in males in the United Kingdom and United States during the years 2000 to 2011.

Materials and Methods

Data sources

Our UK sample came from the Clinical Practice Research Datalink (CPRD), a registry of health record information from general practitioners throughout the United Kingdom. Clinical diagnoses and procedures, written prescriptions, and laboratory results were evaluated in the years 2000 to 2011.

Our US sample was based in the MarketScan Commercial Claims and Encounters and Medicare Supplementary and Coordination of Benefit databases (Truven Healthcare Analytics) for the years 2000 to 2011, which contain insurance billing claims from employer-based insurance plans from approximately 100 larger employers from throughout the United States. The databases contain patient-level information on inpatient and outpatient procedures and diagnoses as well as pharmacy dispensing information for commercially insured employees and dependents as well as retirees with employer-based Medicare supplemental insurance. Outpatient laboratory assay results were available during the years 2007 to 2011 for a subset of patients whose assays were processed by a large nationwide laboratory testing corporation.

Testosterone formulations

Our definition of testosterone initiation included injection testosterone, implantable testosterone pellets, transdermal patches and gels, oral/buccal testosterone, and oral methyltestosterone. Injections and implants were identified through outpatient procedure codes (Read codes in the United Kingdom and Current Procedure Terminology [CPT] codes in the United States) or pharmacy medication codes. Pharmacy-dispensed medications were identified from physician prescribing records in the United Kingdom and pharmacy dispensing billing claims using National Drug Codes in the United States.

Testosterone testing

We identified outpatient procedure codes for laboratory measurements of total serum testosterone using procedure Read codes in the United Kingdom and CPT codes in the United States. The UK assays had corresponding result values recorded with the procedure; in the United States, we identified corresponding assay result values where available in the supplemental laboratory files by identifying assay results using Logical Observation Identifiers Names and Codes codes with dates corresponding to the date of the CPT code for the assay.

Where laboratory results were available, we classified the testosterone level as low, normal, or high based on accompanying result flags or assay-specific reference ranges. If result flags or reference ranges were not available, we classified the result based on the following, general reference ranges: low, <300 mg/dL (10.4 nmol/L); normal, 300 to 849 ng/dL (10.4–25.4 nmol/L); and high, ≥850 ng/dL (29.5 nmol/L).

Participants

We identified 2 nonexclusive cohorts of adult (≥18 years) men in each data source: first, men with a new total serum testosterone test; second, all adult men initiating testosterone therapy, regardless of baseline testing. In both cohorts, we required a 180-day baseline/washout period with continuous system enrollment. Patient characteristics were assessed dur-

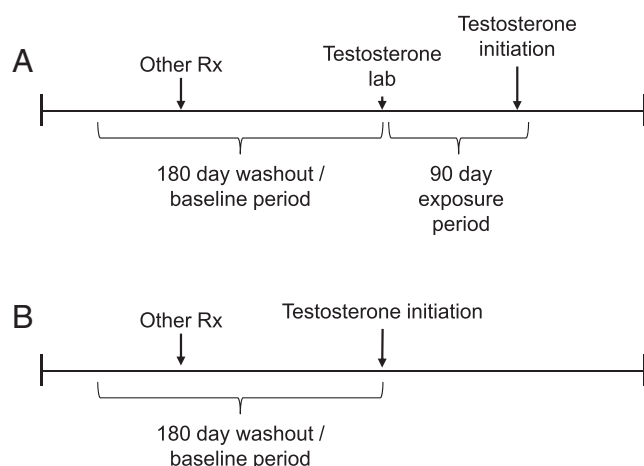


Figure 1. Cohort schematics. A, Testosterone testing cohort. B, Testosterone initiation cohort.

ing the baseline period, including the index date, and they included procedures, diagnoses, medications, and markers of healthcare use. In the US data, we required 1 additional, non-testosterone medication claim during baseline testing to ensure system use for pharmacy benefits.

To calculate population rates of testing and initiation, we measured annual counts of person-years (PY) of eligibility by summing the continuously enrolled person-time of all adult men present on July 1 of each year in each database. These person-time totals were used as denominators in yearly testing and initiation rate calculations.

Testosterone testing cohort

We identified adult men with an outpatient claim for a serum total testosterone test after a 180-day washout period free of testosterone use or testing. We selected the day of the physician's visit during which the test occurred as the index date in the United States and the day the test result was recorded in the patients' record as the index date in the United Kingdom. The 90 days after the code for a testosterone test were considered the exposure period, during which we assessed testosterone initiation in pharmacy dispensing claims (in the United States) or physician prescribing (in the United Kingdom) for testosterone formulations or procedure codes for in-office testosterone injections (Figure 1).

Testosterone initiation cohort

In this initiation cohort, all adult males initiating a testosterone formulation were identified, regardless of whether a baseline testosterone measurement was performed. We established an index date as the date of an in-office injection or implant or pharmacy dispensing/physician prescribing of a testosterone formulation after a 180-day washout period (Figure 1). We recorded any testosterone tests which occurred at any time during the baseline/washout period, but none was required for inclusion, allowing us to identify initiators without recent measurements.

Statistical analysis

Distributions of characteristics were plotted and compared by testosterone status and baseline testosterone levels. Time

trends were displayed by graphing proportions or means of characteristics by year.

We restricted all analyses that required a testosterone level to patients with laboratory values available; all other analyses were performed in the complete cohorts.

Because this was a purely descriptive analysis, no formal hypothesis testing was conducted, and all reported statistics are unadjusted crude estimates. All analyses were performed separately in the 2 national databases. Analyses were performed using SAS version 9.3 (SAS Institute).

This study used deidentified, secondary healthcare data and was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill on July 25, 2012. The protocol was also approved by the Independent Scientific Advisory Committee of the CPRD, Medicines & Healthcare Products Regulatory Agency, on May 17, 2013. Written consent was not required from study participants.

Results

We identified 410 019 US men and 6858 UK men who initiated a testosterone formulation during the study period. We also identified 1 114 329 eligible men with a claim for a testosterone test in the United States and 66 140 in the United Kingdom.

Testosterone testing

The characteristics of men receiving new laboratory tests for total serum testosterone are shown in Table 1. Although mean age was generally similar between the samples from the two nations, the United Kingdom tended to test more men over age 65 than the United States. Tested men in the United States tended to have higher proportions of comorbidities (hypertension, diabetes, and cardiovascular medication use) than those in the United Kingdom. The prevalence of a sexual dysfunction diagnosis was very low in the United States compared with the United Kingdom, likely due to undercoding, because erectile dysfunction drug use was much more similar among the two countries. Fatigue was a common diagnosis before testing in the United States, but it appeared very infrequently in the United Kingdom.

Testosterone testing rates increased over the study period in both countries, with new testing in untreated individuals in the United Kingdom increasing from 13.0/10 000 PY in 2000 to 46.4/10 000 PY in 2010 and from 39.6/10 000 PY in 2000 to 170.0/10 000 PY in the United States in 2010 (Figure 2). Laboratory test result values were not available for all identified index assays performed: there were 2030 (3.1%) missing test results in the United Kingdom; due to the supplemental nature of the laboratory values in the US data, 1 068 693 (95.9%) of the identified tests did not have a corresponding result value. We plotted the covariate distributions of those with

Table 1. Characteristics of Men Undergoing New Testosterone Assays and Initiation in the United Kingdom and United States

Characteristic	Men With New Laboratory Tests		Testosterone Initiators	
	United Kingdom	United States	United Kingdom	United States
n	66 140	1 114 329	6833	410 019
Mean age (SD), y	52.7 (14.2)	50.2 (11.5)	54.1 (14.1)	52.1 (11.8)
18–39 y	18.0%	17.7%	15.6%	12.4%
40–64 y	61.5%	76.5%	61.0%	74.0%
≥65 y	20.5%	5.8%	23.4%	13.6%
Mean number of prior testosterone laboratory tests (SD)			0.63 (0.81)	0.71 (0.69)
Hypogonadism/low testosterone diagnosis	0.2%	9.7%	11.8%	39.9%
Sexual dysfunction	47.4%	0.1%	23.6%	0.2%
Fatigue	0.7%	19.8%	1.0%	20.4%
Hypertension	2.5%	28.7%	2.5%	32.7%
Diabetes	3.2%	15.1%	5.9%	19.6%
Prostate cancer screening	24.9%	54.4%	19.9%	39.8%
Statin use	14.6%	24.6%	19.8%	34.3%
β-Blocker use	7.2%	11.9%	8.2%	16.6%
ACEi use	10.8%	17.2%	13.1%	22.3%
ARB use	3.9%	8.9%	4.9%	12.4%
Thiazide diuretic use	6.1%	12.7%	6.1%	17.1%
NSAID use	12.1%	10.5%	13.0%	14.6%
PPI use	11.7%	10.9%	14.6%	15.7%
Erectile dysfunction drug use	15.3%	10.4%	15.4%	14.6%

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; PPI, proton pump inhibitor.

laboratory results available and those without, and no differences between the groups were observed in either country (data not shown).

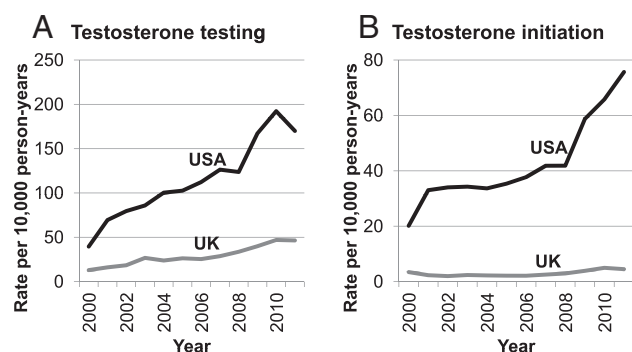
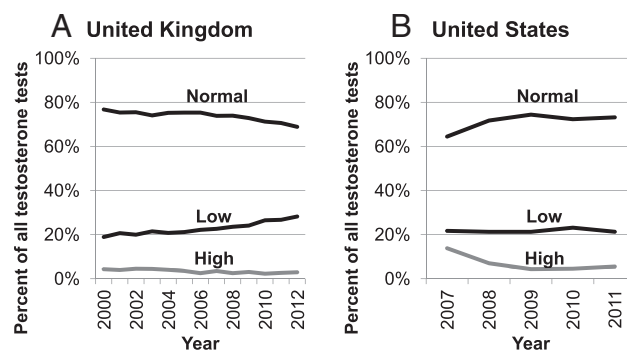
The proportion of tested men with low assay results in the United Kingdom increased from 18.9% in 2000 to 26.7% in 2011, with corresponding declines in normal and high assay results. In contrast, the proportion of low results in the United States stayed constant over the time period, whereas the proportion of normal results increased slightly from 64.5% to 73.2% (laboratory results were only available from 2007–2011) (Figure 3).

The proportion of men in each level of pretreatment total testosterone who initiated a testosterone formulation

within 90 days of the assay differed greatly between the two nations. In the United Kingdom, about 10% of those with low levels initiated testosterone, and this proportion remained constant from 2000 to 2011. In the United States, the same proportion increased from 36% to 43% from 2007 to 2011 (Figure 4). Those with normal or high levels received testosterone in approximately 1% or less of cases in the United Kingdom, whereas the United States treated such individuals in 4% to 9% of cases.

Testosterone initiation

When considering all initiators regardless of the presence of a recent laboratory measurement, initiators of tes-

**Figure 2.** Trends of testosterone laboratory testing (A) and initiation (B) in the United States and United Kingdom, 2000 to 2011.**Figure 3.** Serum total testosterone laboratory test results by year among newly tested non-testosterone users in the United Kingdom (A) and United States (B).

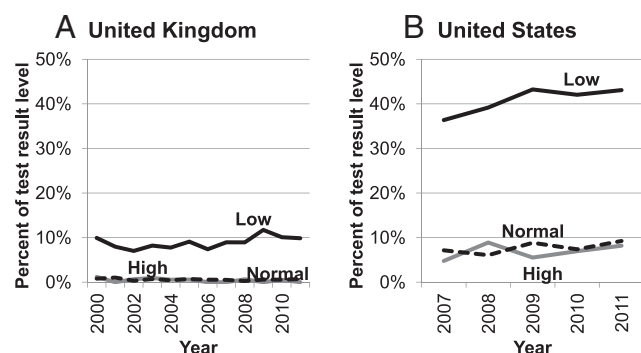


Figure 4. The 90-day initiation of testosterone rates by baseline testosterone level in the United Kingdom (A) and United States (B).

tosterone in the United Kingdom and United States were of comparable ages, but again, a greater proportion of treatment tended to happen in men over 65 in the United Kingdom compared with the United States. The UK initiators tended to have fewer comorbidities and less comedication use (Table 1). Similarly to the testing cohort, UK initiators had vastly more diagnoses of sexual dysfunction, although erectile dysfunction medication use was comparable between the two populations. Fatigue diagnoses were common in the United States but not in the United Kingdom. In both populations, diagnoses of hypogonadism or testosterone deficiency (irrespective of baseline testing) were lower than would be expected in the 180 days before testosterone initiation but were still substantially higher in the United States (United Kingdom, 11.8%; United States, 39.9%).

We evaluated testosterone testing before initiation. In the United Kingdom, 53.8% of initiators did not have a total testosterone measurement in the 180 days before initiation, 32.7% had 1 test, and the remaining had more than 1 test. US initiators had more testosterone tests immediately before initiation: 40.2% did not have a baseline test, 50.0% had 1 test, and the remaining had more than 1 test.

The rate of testosterone initiation increased dramatically from 2000 to 2011 in the United States, particularly since 2008; the yearly initiation rate increased from 20.2/

10 000 PY to 75.7/10 000 PY from 2000 to 2011. In the United Kingdom, baseline initiation rates were profoundly lower, and the increase was more modest, ranging from 3.4/10 000 PY to 4.5/10 000 PY (Figure 2).

The choice of index testosterone formulation changed drastically in both populations over the course of the study. By the end of the study period, transdermal gels had overtaken injections and patches as the overwhelming initial treatment of choice in both countries. Gel prescriptions increased from 24.5% of initiation treatments in the United States in 2000 to 60.8% in 2008 and then it settled at 54.4% in 2011. After its introduction into UK markets in 2003, testosterone gel rapidly overtook all other formulations as the predominant initial treatment by 2005; by 2013, gel was the initial treatment choice in 69.6% of initiators (Figure 5).

Discussion

The rates of new testosterone testing and supplementation have increased substantially since 2000, with more dramatic increases seen in the United States where testosterone initiation has almost quadrupled. In the United Kingdom, it has only increased by approximately one-third. We documented substantial shifts away from use of injections and patch formulations toward topical gels, which were the overwhelming formulation of choice by the end of the study period.

Additionally, testosterone testing has increased markedly in both the United Kingdom and the United States. Interestingly, however, the increased testing in the United Kingdom seems to be more targeted, identifying more individuals with reduced testosterone levels; the United States seems to be testing more and more men with normal levels. Heavy direct-to-consumer marketing of newer testosterone formulations in the United States may have led to a much wider interest in testosterone levels and hypogonadism symptoms, resulting in wider testing of men with nonspecific symptoms but normal levels rather than targeted testing of symptomatic individuals.

Although increases in use may have resulted from heightened awareness of decreasing testosterone levels in older age, testosterone initiation should not be based on low testosterone measurements alone. Guidelines recommend treating those with symptomatic hypogonadism and discourage general treating of men with natural age-related reduced testosterone unless levels are low upon multiple measurements and symptoms are present (1). However, hypogonadism symptoms can be poorly defined, and diagnoses of sexual dysfunction, fatigue, and hypogonadism were low in both the testing and initiation cohorts. Addi-

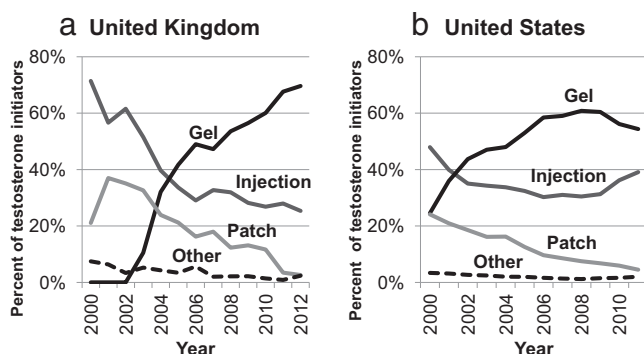


Figure 5. Initial formulation in testosterone initiators.

tionally, the use of sexual dysfunction and fatigue diagnoses seem to vary substantially by country.

Previous research based on UK pharmaceutical dispensing and cost data suggested an increase in testosterone use over the previous decade (15). Although use and costs (primarily due to newer transdermal gels) are increasing, our analysis of person-level clinical data suggests that new initiation is still quite restrained in the United Kingdom, occurring primarily in those with low testosterone levels, unlike the United States, where large increases in the proportion of US middle-aged and elderly men receiving testosterone have been reported (16). Our study suggests that increases in US testosterone use are accompanied by increases in less-targeted testing; the wider use seen in the United States occurs among men at all testosterone levels; and in both the United States and the United Kingdom, inadequate lab measurement seems to be occurring before initiation. It appears that nonindicated use of testosterone is widespread. In the United States, heavy direct-to-consumer marketing, the rise of specialty male hormone clinics, and other factors have led to a much wider interest in low testosterone in the general public. Standardized internet search trend data from Google Trends (<http://www.google.com/trends/explore#q=low%20testosterone&geo=US%2C%20GB&cmpt=geo>, accessed on November 6, 2013) demonstrates that the US searches for information about low testosterone almost 4 times more often than the United Kingdom, suggesting much greater awareness of and potentially more patient requesting of testosterone testing and treatment.

The observed increases in use are potentially troubling in light of recent reports of increased risks associated with testosterone use: death, myocardial infarction, and stroke in an observational study of older men with cardiovascular disease and hypogonadism (30) and cardiovascular events from a meta-analysis of testosterone trials (31). With the observed increased risk of adverse events (30, 32), expanded use into populations without established medical necessity could be potentially dangerous.

Our study relies upon secondary healthcare data that contain inherent limitations. Testosterone measurement results can vary widely within individuals (33) and by the type of assay performed. We used assay-specific reference ranges and result flags that accompany the assay result whenever possible to categorize the results. However, these references were missing in many cases, requiring us to apply a standard set of reference ranges that may not accurately categorize true testosterone level, possibly causing misclassification in some cases. However, the result information available to us reflects the information available to a prescribing physician, where a single measurement result may be vague or inconclusive. Addition-

ally, categorizing one's testosterone level based on 1 measurement alone may be overly simplistic, and guidelines recommend multiple tests to confirm low testosterone status (1). However, in our observed population of testosterone initiators, the vast majority of users in both populations had fewer than 2 recent tests before initiation, indicating widespread initiation outside of published guidelines.

We observed a high proportion of initiators without a baseline lab assay in the 180 days before initiation. Although many men may be initiating therapy without baseline assays, we may not be observing all baseline assays in individuals. Test results may be received outside of the traditional clinic environment and paid out of pocket in the United States or measured by a specialist and failed to be reported back to the general practitioner in the United Kingdom. Additionally, some physicians may adopt a wait-and-see approach, where testosterone treatment doesn't immediately follow a laboratory test or follow-up appointments or referral to specialty care may take longer than 90 days, and therefore, the test may have been recorded before our assessment period, causing us to overestimate the amount of prescribing without baseline testing. It is also possible that we failed to identify the true initiation of testosterone. Testosterone may be used intermittently with large gaps in treatment; therefore, some of our initiators may actually be reinitiators with testosterone assays or previous use periods before our observed baseline period.

Testosterone measurement results were only available for a subset of men in the United States, although the presence of tests without results could be observed from billing codes for serum testosterone tests. In all measured characteristics, men with lab results available were very similar to men with tests observed but results not available, suggesting our US sample of men with measured testosterone levels is generally representative of the employer-insured adult male population. There are men in the United States without employer-based insurance or Medicare supplemental plans to whom our study may not be generalizable; however, the CPRD is highly representative of the general practice setting throughout the United Kingdom.

Our study benefited from a very large diverse sample of men from throughout the United Kingdom and United States. In these men, we observed sharp increases in testosterone testing and initiation. Particularly in the United States, we observed increasing testing in men without low testosterone levels, suggesting a larger societal awareness of and interest in low testosterone as a diagnosis. We observed a large proportion of men initiating testosterone therapy without a clear indication for treatment. In such

a setting with limited evidence of efficacy and unresolved safety concerns, the medical necessity for testosterone treatment should be closely considered before initiation. Further research is required to determine the safety of the use of testosterone in men with only minimally reduced or normal testosterone levels.

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References

1. 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;95:2536–2559.
2. Travison TG, Araujo AB, Hall SA, McKinlay JB. Temporal trends in testosterone levels and treatment in older men. *Curr Opin Endocrinol Diabetes Obes*. 2009;16:211–217.
3. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab*. 2001;86:724–731.
4. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab*. 2002;87:589–598.
5. Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab*. 2008;93:2737–2745.
6. Araujo AB, Esche GR, Kupelian V, et al. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab*. 2007;92:4241–4247.
7. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006;60:762–769.
8. Iglesias P, Carrero JJ, Díez JJ. Gonadal dysfunction in men with chronic kidney disease: clinical features, prognostic implications and therapeutic options. *J Nephrol*. 2012;25:31–42.
9. Liverman CT, Blazer DG, eds. *Testosterone and Aging: Clinical Research Directions*. Washington, DC: The National Academies Press; 2004.
10. Basaria S. Testosterone therapy in older men with late-onset hypogonadism: a counter-rationale. *Endocr Pract*. 2013;19:853–863.
11. Delamothe T. Monkey business: reflections on testosterone. *BMJ*. 2012;345:e4967.
12. Gan EH, Pattman S, Pearce S, Quinton R. Many men are receiving unnecessary testosterone prescriptions. *BMJ*. 2012;345.
13. Hackett G, Kirby M, Jackson G, Wylie K. Evidence based medicine inevitably increases testosterone prescribing. *BMJ*. 2012;345.
14. Gorricho J, Gavilán E, Gervas J. Marketing, not evidence based arguments, has probably increased testosterone prescribing. *BMJ*. 2012;345:e6905.
15. Gan EH, Pattman S, Pearce S, Quinton R. A UK epidemic of testosterone prescribing, 2001–2010. *Clin Endocrinol (Oxf)*. 2013;79:564–570.
16. Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med*. 2013;173:1465–1466.
17. Handelsman DJ. Pharmacoepidemiology of testosterone prescribing in Australia, 1992–2010. *Med J Aust*. 2012;196:642–645.
18. Handelsman DJ. Global trends in testosterone prescribing, 2000–2011: expanding the spectrum of prescription drug misuse. *Med J Aust*. 2013;199:548–551.
19. Wang C, Nieschlag E, Swerdloff RS, et al. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male*. 2009;12:5–12.
20. Lazarou S, Reyes-Vallejo L, Morgentaler A. Wide variability in laboratory reference values for serum testosterone. *J Sex Med*. 2006;3:1085–1089.
21. McShane LM, Dorgan JF, Greenhut S, Damato JJ. Reliability and validity of serum sex hormone measurements. *Cancer Epidemiol Biomarkers Prev*. 1996;5:923–928.
22. Yun YM, Botelho JC, Chandler DW, et al. Performance criteria for testosterone measurements based on biological variation in adult males: recommendations from the Partnership for the Accurate Testing of Hormones. *Clin Chem*. 2012;58:1703–1710.
23. Finkelstein JS, Lee H, Burnett-Bowie SA, et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med*. 2013;369:1011–1022.
24. Jick H, Wilson A. The cost of prescription drugs: a comparison of two countries. *Pharmacotherapy*. 2012;32:967–969.
25. Jick H, Wilson A, Wiggins P, Chamberlain DP. Comparison of prescription drug costs in the United States and the United Kingdom, part 2: proton pump inhibitors. *Pharmacotherapy*. 2012;32:489–492.
26. Jick H, Wilson A, Wiggins P, Chamberlain DP. Comparison of prescription drug costs in the United States and the United Kingdom, part 3: methylphenidate. *Pharmacotherapy*. 2012;32:970–973.
27. Jick H, Wilson A, Wiggins P, Chamberlain DP. Comparison of prescription drug costs in the United States and the United Kingdom, Part 1: statins. *Pharmacotherapy*. 2012;32:1–6.
28. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363:109–122.

29. Basaria S, Davda MN, Travison TG, Ulloor J, Singh R, Bhasin S. Risk factors associated with cardiovascular events during testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci*. 2013;68:153–160.
30. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013;310:1829–1836.
31. Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013;11:108.
32. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol A Biol Sci Med Sci*. 2005;60:1451–1457.
33. Collier CP, Morales A, Clark A, Lam M, Wynne-Edwards K, Black A. The significance of biological variation in the diagnosis of testosterone deficiency, and consideration of the relevance of total, free and bioavailable testosterone determinations. *J Urol*. 2010;183:2294–2299.



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