Who Gets Testosterone? Patient Characteristics Associated with Testosterone Prescribing in the Veteran Affairs System: a Cross-Sectional Study

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BACKGROUND: There has been concern about the growing off-label use of testosterone. Understanding the context within which testosterone is prescribed may contribute to interventions to improve prescribing.

OBJECTIVE: To evaluate patient characteristics associated with receipt of testosterone.

DESIGN: Cross-sectional.

SETTING: A national cohort of male patients, who had received at least one outpatient prescription within the Veterans Affairs (VA) system during Fiscal Year 2008–Fiscal Year 2012.

PARTICIPANTS: The study sample consisted of 682,915 non-HIV male patients, of whom 132,764 had received testosterone and a random 10% sample, 550,151, had not.

MAIN MEASURES: Conditions and medications associated with testosterone prescription.

KEY RESULTS: Only 6.3% of men who received testosterone from the VA during the study period had a disorder of the testis, pituitary or hypothalamus associated with male hypogonadism. Among patients without a diagnosed disorder of hypogonadism, the use of opioids and obesity were the strongest predictors of testosterone prescription. Patients receiving >100 mg/equivalents of oral morphine daily (adjusted odds ratio = 5.75, $p < 0.001$) and those with body mass index (BMI) >40 kg/m^2 (adjusted odds ratio = 3.01, $p < 0.001$) were more likely to receive testosterone than non-opioid users and men with BMI <25 kg/m^2. Certain demographics (age 40–54, White race), comorbid conditions (sleep apnea, depression, and diabetes), and medications (antidepressants, systemic corticosteroids) also predicted a higher likelihood of testosterone receipt, all with an adjusted odds ratio less than 2 ($p < 0.001$).

CONCLUSIONS: In the VA, 93.7% of men receiving testosterone did not have a diagnosed condition of the testes, pituitary, or hypothalamus. The strongest predictors of testosterone receipt (e.g., obesity, receipt of opioids), which though are associated with unapproved, off-label use, may be valid reasons for therapy. Interventions should aim to increase the proportion of testosterone recipients who have a valid indication.

KEY WORDS: testosterone; prescribing; patient; predictors.
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INTRODUCTION

The Endocrine Society guidelines recommend that the diagnosis of androgen deficiency should be made by ascertainment of signs and symptoms together with low morning testosterone levels on two or more occasions.[1] We have previously reported that 16.5% of male Veterans Administration Health Care System (VA) patients received this therapy without first undergoing the recommended workup.[2] Our finding and similar findings by others[3] have raised concern among regulatory agencies about potential off-label use of testosterone in conditions for which it is not approved.

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A confluence of factors has heightened the concern of the US Food and Drug Administration[4] (FDA) about the rapid growth of testosterone prescriptions in the US. There has been a substantial increase in the number of prescriptions for men with age-related decline in testosterone, for which therapy is not approved.[5] The long-term risks and benefits of testosterone therapy have not been clearly demonstrated, especially in middle-aged and older men with age-related decline in testosterone. Some reports have suggested an increased risk of cardiovascular events in men prescribed testosterone,[6–8] although other reports differ.[9] Putative contributors to this growth in the US include the direct-to-consumer marketing of testosterone products, along with the failure of some professional society guidelines to distinguish age-related decline from organic hypogonadism due to known diseases of the testis, pituitary, and the hypothalamus.[10]

Here, we determined the proportion of testosterone recipients within the VA who do have such a known diagnosis of the testis, pituitary, and hypothalamus. We then evaluated the characteristics of patients without a formal indication to receive testosterone who had nevertheless received it. Our findings will help us understand who is receiving testosterone and why, which can drive quality improvement efforts to optimize how testosterone is prescribed.

METHODS

The study was approved by the Institutional Review Board of the Bedford VA Medical Center. We examined demographic, diagnostic, and prescription data for patients receiving outpatient medications in the VA from October 1, 2007 to September 30, 2012 (FY08–FY12).

STUDY POPULATION

The initial sample consisted of 810,686 male patients, who had received at least one outpatient prescription filled within the VA during FY08–FY12, identified from VA Pharmacy data (Fig. 1). Though there was no official VA policy on testosterone therapy during the study period, since then the VA's Pharmacy Service has issued Criteria for Use (CFU) for testosterone therapy in adult men.[11]

Our 810,686 participants included all patients who had received at least one testosterone fill during the study period ("testosterone patients," $n = 162{,}092$) and a random 10% sample of patients who had a prescription fill for at least one medication other than testosterone ("non-testosterone patients," $n = 648{,}594$). We excluded 5,817 patients with human immunodeficiency virus (HIV) because the use of testosterone is different in patients with HIV.[12,13] For testosterone patients, the earliest testosterone prescription fill between FY09–12 was used as the index fill. For non-testosterone patients, a fill from FY09–12 was chosen at random to roughly match the time distribution of the testosterone fills. We required a 1-year "look-back" period to assess diagnoses and medications before the index fill for both testosterone and non-testosterone populations. Therefore, we excluded 13,112 patients with fills only in FY2008 and 94,220 individuals who did not have a documented fill in the year prior to the index fill. These maneuvers help establish a cohort of "VA users," or patients who have demonstrated that they use VA for a sizeable part of their care and are therefore likely to have relatively complete data.

IDENTIFYING PATIENTS WITH DIAGNOSED CONDITIONS OF THE TESTIS, PITUITARY, AND THE HYPOTHALAMUS

We first identified all men with diagnosed conditions of the testis (e.g., Klinefelter's syndrome), pituitary (e.g., hyperprolactinemia), and the hypothalamus (e.g., Kallmann's syndrome). These conditions are known to be associated with classical hypogonadism, for which testosterone therapy is approved by the FDA. We determined the presence of such conditions using inpatient and outpatient ICD-9 diagnosis codes (Online Appendix 1). Conditions were deemed present if there were at least two diagnoses separated by 7 or more days.

We excluded patients with classical hypogonadism from further analyses from both the testosterone and non-testosterone samples ($n = 14{,}402$) (Fig. 1). The latter analyses were concerned with which patient characteristics predicted testosterone receipt when the patient did not have a classical indication to receive it. Lastly, we also excluded 220 men with an identified gender identity disorder from both samples because of the likelihood that testosterone was being provided as part of a gender reassignment. Therefore, the final analytical sample consisted of 682,915 non-HIV male patients, of whom 132,764 had received testosterone and 550,151 had not.

DEPENDENT VARIABLE: TESTOSTERONE PRESCRIBING

Our primary outcome was whether or not the patient received testosterone from an outpatient VA pharmacy during the study period, including all forms of testosterone (injectable, transdermal, etc.). We obtained medication data from the VA Pharmacy Benefits Management Services.

INDEPENDENT VARIABLES: SOCIO-DEMOGRAPHICS

We examined socio-demographics as predictors of testosterone receipt, including age, marital status, copayment, race/ethnicity, and zip code of residence, since these have all been linked to healthcare utilization.[14] We expected married patients to use more healthcare in general and also to be more likely to report sexual symptoms. The requirement for a copayment for a prescription would be expected to reduce

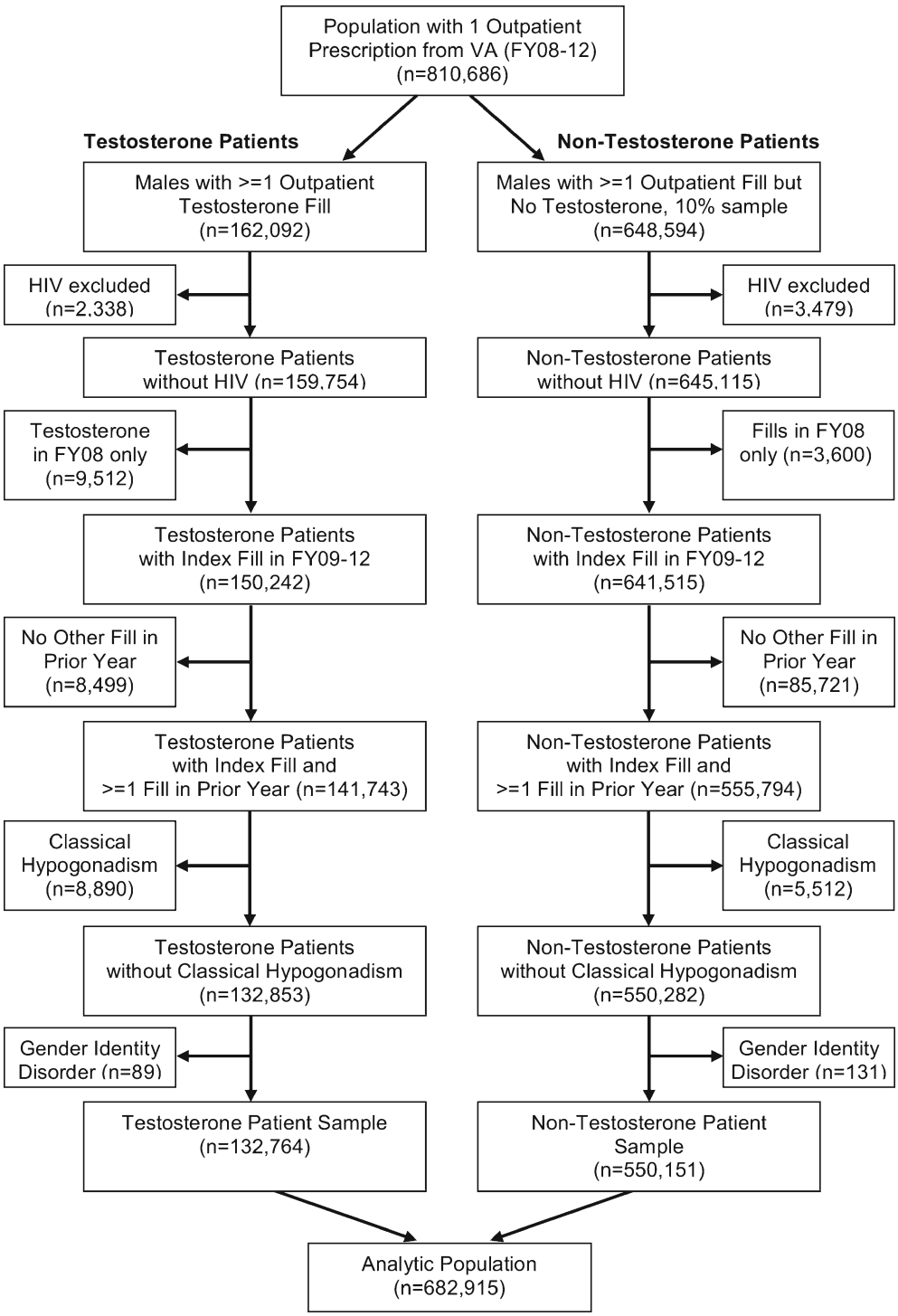

Fig. 1 STROBE diagram of the analytic population, $n = 682,915$. *HIV* Human immunodeficiency virus, *FY* fiscal year

utilization. We also expected testosterone prescribing rates to differ by race and hypothesized that African American males would be less likely to receive testosterone, due to either patient preferences and/or differing recommendations by providers.[15] The patient's zip code of residence was linked to US Census data to obtain the percentage of people living below the federal poverty line in each geographic area, which is a proxy measure for socioeconomic status.[16].

INDEPENDENT VARIABLES: COMORBID CONDITIONS AND MEDICATIONS

We evaluated the association of testosterone receipt with a number of conditions and medications using data from the VA Corporate Data Warehouse (CDW). A 1-year "look-back" period was used to check for conditions and medications that occurred before the date of the index prescription for both testosterone and non-testosterone patients. Presence of these

conditions was determined from inpatient and outpatient diagnoses using ICD-9 codes (Online Appendix 1). The criterion was occurrence of at least two diagnoses separated by seven or more days.

We examined physical conditions that have been related to low testosterone levels, including diabetes,[17] obesity,[18] cardiovascular disease and its risk factors,[19] sleep apnea,[20] stroke,[21] kidney disease,[22] liver disease,[23] and prostate cancer.[24] We also examined mental health conditions that have been linked with low testosterone levels, including depression,[25] dementia,[26] schizophrenia,[27] and alcohol abuse.[28]

We assessed obesity as a predictor, stratifying patients by body mass index (BMI). Higher BMI is associated with low sex-hormone-binding protein (SHBG), which could lower total testosterone levels. Since we have already examined the adequacy of laboratory workups prior to testosterone receipt in a separate report,[2] laboratory tests such as testosterone levels were not extensively considered in this study.

In addition to these conditions, we also evaluated the use of four medication classes (opioids, antidepressants, antipsychotics, and systemic glucocorticoids) as possible predictors of testosterone receipt, because they depress endogenous testosterone levels or because they may be linked with testosterone therapy through other mechanisms.[29–31] We computed the mean daily dose of opioids for each patient during the year prior to the index prescription, expressed in mg/morphine equivalents (Online Appendix 2a). We expected higher opioid doses to be associated with increasing testosterone use. Online Appendix 2b details the specific medications included in each medication category.

Table 1 Prevalence of Classical Hypogonadism Among Testosterone and Non-Testosterone Patients

	Testosterone N %		Non-testosterone N %	
Total	141,743	100.0%	555,794	100.0%
Any classical hypogonadism	8890	6.3%	5512	1.0%
Any testicular condition	2468	1.7%	4361	0.8%
Mumps orchitis	1269	0.9%	3167	0.6%
Neoplasm of testis	644	0.5%	554	0.1%
Klinefelter's syndrome	402	0.3%	26	0.0%
Orchiectomy	182	0.1%	648	0.1%
Undescended testis (cryptorchidism) or retractile	50	0.0%	40	0.0%
Gonadal dysgenesis	15	0.0%	1	0.0%
Any pituitary condition	3703	2.6%	977	0.2%
Neoplasms of pituitary	3021	2.1%	535	0.1%
Hyperprolactinemia	767	0.5%	139	0.0%
Hypophysectomy	240	0.2%	20	0.0%
Pituitary surgery	150	0.1%	12	0.0%
Hemochromatosis	119	0.1%	336	0.1%
Optic chiasmus w/ pituitary disease	30	0.0%	4	0.0%
Any hypothalamic condition	4109	2.9%	243	0.0%
Kallmann's syndrome	2571	1.8%	165	0.0%
Idiopathic hypogonadotropic hypogonadism	1743	1.2%	81	0.0%
No classical hypogonadism	132,853	93.7%	550,282	99.0%

STATISTICAL ANALYSES

Missing values on continuous variables were supplemented by multiple imputation using all covariates. The percentage of patients with missing data was 4.9% for BMI, 2.3% for the measure of poverty in patient's zip code, and 0.9% for age. The category "unknown" was considered separately for race/ethnicity and marital status.

Since the non-testosterone sample consisted of a random 10% of the entire population, a weight of 10 was applied to this sample for the computation of proportions (but not the generation of odds ratios). Logistic regression was used to ascertain the likelihood of being on testosterone as a function of patient characteristics. Both bivariate and multivariate ("fully adjusted") models were generated. Given the large number of observations, a level of $p < 0.001$ was considered statistically significant. Analyses were conducted using SAS, version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Patients with Diagnosed Conditions of the Testis, Pituitary, and the Hypothalamus

Of 141,743 patients who received testosterone at least once during the 5-year study period, 8,890 (6.3%) had a diagnosed condition of the testis, pituitary, or the hypothalamus (Table 1): 1.7% had a testicular, 2.6% a pituitary, and 2.9% a hypothalamic condition. These conditions were not present in 93.7% of testosterone and 99.0% of non-testosterone patients.

Patient Socio-Demographics Associated with Testosterone Prescription

Table 2 displays the socio-demographics of patients without a diagnosed condition of the testes, pituitary, or hypothalamus. Percentages are weighted to reflect the entire VA population. Nearly half of the men (50.3%) in our weighted sample were age 50–69 years. Most patients were White non-Hispanics (72.1%). Approximately 55% were married, and 73.5% had copayments to receive medication.

In the fully adjusted model, men age 40–54 years were most likely to receive testosterone, while those under 40 years [adjusted odds ratio (AOR) = 0.67; for this and all other findings discussed here, $p < 0.001$] and those over 80 years (AOR = 0.37) were considerably less likely. Hispanic and Black non-Hispanics were less likely to receive testosterone compared to White non-Hispanics (AOR = 0.61 and 0.72, respectively). Compared to married men, other men were less likely to receive testosterone, including divorced/separated

Table 2 Patient characteristics and association with being on testosterone ($n = 682,915$)

Variable	Number of patients (weighted %)†	Odds ratio (95% CI)*	
		Unadjusted	Fully adjusted‡ (c = 0.734)
Age (c = 0.610)			
20–39	64,794 (10.0%)	0.53* (0.52–0.54)	0.67* (0.66–0.69)
40–49	74,809 (10.4%)	0.97 (0.95–0.99)	1.10* (1.07–1.12)
50–54	62,944 (8.8%)	0.96* (0.94–0.98)	1.05* (1.03–1.08)
55–59	119,379 (16.4%)	1.04* (1.02–1.06)	1.00 (0.98–1.02)
60–64	120,148 (16.6%)	ref.	ref.
65–69	58,693 (8.5%)	0.77* (0.76–0.79)	0.93* (0.90–0.95)
70–74	58,713 (9.1%)	0.51* (0.50–0.53)	0.70* (0.68–0.72)
75–79	55,892 (9.0%)	0.36* (0.35–0.37)	0.54* (0.52–0.56)
80–99	67,543 (11.3%)	0.21* (0.21–0.22)	0.37* (0.36–0.39)
Race/ethnicity (c = 0.534)			
White, non-Hispanic	500,244 (72.1%)	ref.	ref.
Black, non-Hispanic	95,677 (14.7%)	0.68* (0.67–0.69)	0.72* (0.71–0.74)
Hispanic	8397 (1.3%)	0.52* (0.48–0.55)	0.61* (0.57–0.65)
Other, specified	16,429 (2.4%)	0.86* (0.83–0.90)	0.79* (0.76–0.83)
Unknown	62,168 (9.4%)	0.73* (0.72–0.75)	0.95* (0.92–0.97)
Marital status (c = 0.551)			
Married	385,355 (55.0%)	ref.	ref.
Divorced or separated	175,365 (25.8%)	0.86* (0.84–0.87)	0.80* (0.79–0.81)
Never married	65,936 (10.4%)	0.52* (0.51–0.53)	0.60* (0.59–0.62)
Widowed	48,070 (7.6%)	0.48* (0.47–0.49)	0.73* (0.71–0.76)
Unknown	8,189 (1.2%)	0.82* (0.78–0.87)	0.86* (0.81–0.92)
Percent poverty in zip code of residence (c = 0.523)			
0–10%	197,173 (29.0%)	ref.	ref.
10–20%	302,160 (43.7%)	1.09* (1.08–1.11)	1.02 (1.00–1.03)
20–30%	129,978 (19.0%)	1.02 (1.00–1.04)	0.97 (0.95–0.99)
30%+	53,604 (8.3%)	0.69* (0.67–0.71)	0.76* (0.74–0.78)
Copayment required when obtain medication? (c = 0.570)			
Yes	485,503 (73.5%)	0.53* (0.52–0.54)	0.81* (0.80–0.82)
No	197,412 (26.5%)	ref.	ref.

**Odds ratio differs from the reference group, that is, patients without the specified factor, at the level of $P < 0.001$. All other odds ratios do not differ from the reference group at the 0.001 level*

†Percentage calculation takes into account the fact that we used a 10% random sample of non-testosterone patients

‡The fully adjusted model employs the following independent factors: age, race/ethnicity, marital status, % poverty in patient's zip code area, BMI, whether copayment was required when the patient obtained medication, cancer other than of the prostate, chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes, hyperlipidemia, hypertension, chronic kidney disease, chronic liver disease, sleep apnea, peripheral artery disease, prostate cancer, stroke, transient ischemic attack (TIA), alcohol abuse, anxiety disorder, bipolar disorder, dementia, chronic depression, post-traumatic stress disorder (PTSD), schizophrenia, substance abuse, other psychotic disorders, and prescription of certain medications (anti-depressants, anti-psychotics, glucocorticoids, opioids)

(AOR = 0.80), never married (AOR = 0.60), and widowed (AOR = 0.73). Men residing in zip codes with more than 30% of residents living in poverty were less likely to receive testosterone (AOR = 0.76 compared to less than 10% poverty). Patients who had a copayment for medications were less likely to receive testosterone compared to those with no copay (AOR = 0.81).

Comorbid Conditions and Medications Associated with Testosterone Use

We examined several conditions that we expected might be associated with receipt of testosterone (Table 3). Testosterone receipt was more likely in patients with sleep apnea (AOR = 1.79), hyperlipidemia (AOR = 1.43), depression (AOR = 1.38), bipolar disorder (AOR = 1.34), diabetes (AOR = 1.28), hypertension (AOR = 1.25), anxiety disorder (AOR = 1.18), and post-traumatic stress disorder (AOR = 1.10). Some conditions, such as prostate cancer (AOR = 0.28), stroke (AOR = 0.67), dementia (AOR = 0.76), and heart failure (AOR = 0.83), were associated with lower likelihood of receiving testosterone.

We also examined which patients did not have testosterone levels checked before receiving testosterone, an omission that is contrary to clinical guidelines.[1] Of patients who received testosterone ($n = 132,764$), 20.6% did not have any levels checked, and 5.3% had at least one testosterone level, but it was not low; 54.5% had documentation of only one low level (total testosterone <300 ng/dl or free testosterone <70 pg/ml), and 19.6% had two or more low levels, as required by guidelines. Further, as reported in Table 3, among patients receiving testosterone, patients with diagnoses of substance use and sleep apnea had a greater likelihood of having recorded two or more low testosterone levels before starting therapy ($p < 0.001$ for both). We also examined testosterone testing as an independent predictor of testosterone prescribing, stratifying the analytical sample ($n = 682,915$) into men who had at least one low level and those who did not. Results were generally similar to the main findings and are reported in Online Appendix 3.

Table 3 also shows the medications we examined for possible associations with receipt of testosterone. Opioid use was the most highly associated with testosterone (AOR = 1.70 compared

Table 3 Association of Comorbid Conditions and Medications with Testosterone Receipt ($n = 682,915$)

	Testosterone ($n = 132,764$)	Non-testosterone ($n = 550,151$)	Testing of testosterone level*	Unadjusted	Fully adjusted† (c = 0.733)
Cancer other than prostate	3.3%	3.1%	24.3%	1.07‡ (1.04–1.11)	0.98 (0.95–1.02)
CHF	3.2%	2.9%	21.3%	1.10‡ (1.06–1.14)	0.83‡ (0.80–0.86)
COPD	10.3%	8.0%	21.2%	1.33‡ (1.30–1.36)	1.10‡ (1.07–1.12)
Coronary artery disease	13.8%	11.4%	20.6%	1.24‡ (1.22–1.26)	0.91‡ (0.89–0.93)
Diabetes	33.9%	21.0%	21.4%	1.94‡ (1.91–1.96)	1.28‡ (1.26–1.30)
Hyperlipidemia	47.6%	31.7%	22.3%	1.96‡ (1.93–1.98)	1.43‡ (1.41–1.45)
Hypertension	53.5%	39.9%	21.5%	1.73‡ (1.71–1.76)	1.25‡ (1.23–1.27)
Kidney disease, chronic	3.4%	2.9%	22.2%	1.18‡ (1.14–1.22)	1.01 (0.97–1.05)
Liver disease, chronic	0.9%	0.7%	24.6%	1.23‡ (1.15–1.31)	0.97 (0.91–1.04)
Obstructive sleep apnea	3.3%	0.9%	26.9%	3.65‡ (3.50–3.80)	1.79‡ (1.71–1.87)
Peripheral artery disease	2.8%	2.9%	21.7%	0.97 (0.93–1.00)	0.84‡ (0.81–0.88)
Prostate cancer	0.8%	2.9%	21.2%	0.26‡ (0.25–0.28)	0.28‡ (0.26–0.30)
Stroke	1.4%	1.9%	22.6%	0.75‡ (0.71–0.79)	0.67‡ (0.63–0.70)
TIA	0.4%	0.3%	19.7%	1.15 (1.05–1.27)	1.03 (0.93–1.14)
Alcohol abuse	4.7%	5.8%	25.3%	0.80‡ (0.78–0.82)	0.64‡ (0.62–0.67)
Anxiety disorder	8.4%	4.9%	24.2%	1.78‡ (1.74–1.82)	1.18‡ (1.15–1.21)
Bipolar disorder	4.4%	2.6%	24.7%	1.71‡ (1.66–1.76)	1.34‡ (1.29–1.39)
Dementia	0.4%	0.8%	22.2%	0.53‡ (0.49–0.58)	0.76‡ (0.69–0.84)
Depression, chronic	23.9%	12.6%	24.1%	2.19‡ (2.15–2.22)	1.38‡ (1.36–1.41)
Other psychotic disorders	0.5%	0.6%	22.7%	0.78‡ (0.72–0.85)	0.79‡ (0.72–0.87)
PTSD	17.3%	9.6%	23.4%	1.98‡ (1.94–2.01)	1.10‡ (1.08–1.13)
Schizophrenia	1.2%	1.7%	24.2%	0.73‡ (0.69–0.77)	0.73‡ (0.69–0.78)
Substance abuse	2.4%	3.1%	28.1%	0.77‡ (0.74–0.80)	0.82‡ (0.78–0.85)
Anti-depressants	46.7%	29.6%	21.6%	2.08‡ (2.05–2.10)	1.37‡ (1.35–1.40)
Anti-psychotics	9.5%	7.1%	23.8%	1.37‡ (1.34–1.40)	0.94‡ (0.91–0.96)
Glucocorticoids, systemic	20.8%	16.0%	22.5%	1.38‡ (1.36–1.40)	1.15‡ (1.13–1.17)
Opioids	40.6%	23.6%	21.6%	2.22‡ (2.19–2.24)	1.70‡ (1.68–1.73)

CHF chronic heart failure, COPD chronic obstructive pulmonary disease, TIA = transient ischemic attack, PTSD post-traumatic stress disorder
**Results are only for patients on testosterone. Values refer to percentage of patients with laboratory results indicating two or more low levels of testosterone in the year prior to the earliest testosterone fill. Low testosterone was defined as free T <70 pg/ml or total T <300 ng/dl*
†See note in Table 2
‡Odds ratio differs from the reference group, that is, patients without the specified factor, at the level of P< 0.001. All other odds ratios do not differ from the reference group at the 0.001 level

to no opioids), followed by antidepressants (AOR = 1.37) and systemic glucocorticoids (AOR = 1.15).

Within the group of men who received any opioids, receiving a higher dose was strongly associated with testosterone receipt (Fig. 2a). Men receiving a dose greater than 100 mg/day morphine equivalents had nearly six times the odds of receiving testosterone compared to patients receiving no opioids in the fully adjusted model (AOR = 5.75).

The degree of adiposity, measured as BMI, was also associated with testosterone receipt (Fig. 2b). After adjusting for covariates, patients with morbid obesity (BMI >40 kg/m^2) were much more likely to receive testosterone than normal-weight patients (AOR = 3.01).

DISCUSSION

Only 6.3% of men receiving testosterone prescriptions within the VA had a diagnosed condition of the testis, pituitary, or the hypothalamus; the vast majority of testosterone recipients did not have an approved indication. Among those without a diagnosed condition, the men most likely to receive testosterone were middle-aged men with obesity who had comorbid conditions such as obstructive sleep apnea, depression, or diabetes or who were using medications such as opioids, anti-depressants, or glucocorticoids. Testosterone therapy may be justifiable in patients with some of these conditions, such as men receiving opioids, who may suffer from opioid-induced suppression of testosterone levels[32] and sexual dysfunction,[33] osteoporosis, and/or muscle atrophy.[34] However, the risks and benefits of testosterone in these conditions have not been demonstrated, and therapy is not approved by the FDA for these indications. Even after excluding men receiving opioids or glucocorticoids, the majority of testosterone prescriptions within the VA were written for unapproved off-label indications, for which the risks and benefits are unknown and for which therapy is not approved. Potential contributors to this overprescribing of testosterone include commercial advertising and lax definition of "hypogonadism" by some society guidelines that fails to distinguish between true pathological hypogonadism (for which testosterone therapy is approved) and the mere presence of low testosterone levels.[10] A public health campaign may be necessary to counteract such advertising, correct such deficiencies in treatment guidelines, and improve prescribing.

Opioid medications suppress testosterone levels,[32] and their use is associated with a high prevalence of sexual dysfunction[35] and osteoporosis.[34] Therefore, it is not surprising that the odds for receipt of testosterone were six times more in those patients on high-dose opioids. Our results suggest that opioid therapy may be an important contributor to the increasing use of testosterone in VA.

Both obesity and diabetes are associated with low SHBG, which may lower total testosterone levels.[18,36] Men with obesity or diabetes mellitus typically have low total testosterone

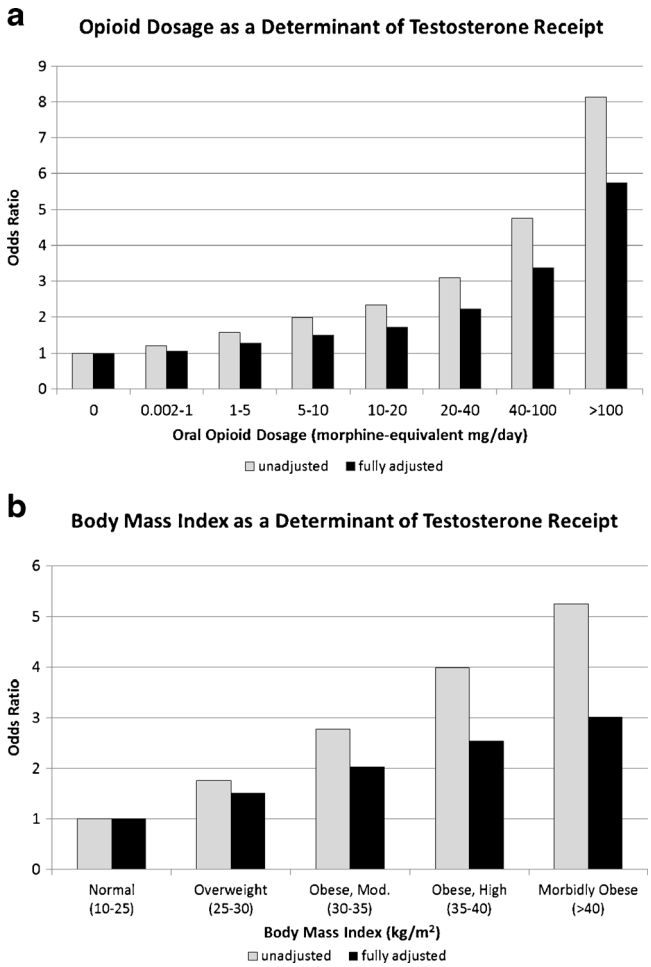

Fig. 2 Opioid dosage and body mass index as determinants of testosterone receipt. The fully adjusted model employs the following independent factors: age, race/ethnicity, marital status, % poverty in patient's zip code area, BMI, whether copayment was required when patient obtained medication, cancer other than of prostate, heart failure, chronic obstructive pulmonary disease (COPD), coronary artery disease, diabetes, hyperlipidemia, hypertension, chronic kidney disease, chronic liver disease, sleep apnea, peripheral artery disease, prostate cancer, stroke, transient ischemic attack (TIA), alcohol abuse, anxiety disorder, bipolar disorder, dementia, chronic depression, posttraumatic stress disorder (PTSD), schizophrenia, substance abuse, other psychotic disorders, and prescription of certain medications (anti-depressants, anti-psychotics, glucocorticoids, opioids). a Opioid dosage. Odds Ratio: Relative to no opioids b Body mass index (BMI). Odds ratio: relative to normal BMI

levels but normal free testosterone, although men with severe obesity and some patients with diabetes may also have low free testosterone levels. The likelihood of receiving a testosterone prescription was also positively associated with BMI in a linear fashion. It might be possible that men with obesity and diabetes, who have a low total testosterone level, may not be hypogonadal and do not need testosterone therapy. Clinical guidelines emphasize the need to measure free testosterone levels, rather than total testosterone, in obese or diabetic patients.[1] In our study, only 27.6% of obese men, who were on testosterone, had one or more documented low circulating free testosterone levels (<70 pg/ml). This may also be an important opportunity to improve clinical practice.

Findings from our study do suggest that some VA providers are doing things that are guideline-concordant, at least some of the time. For example, reduced likelihood of testosterone prescribing among the very old and those with heart failure suggests that VA providers may be employing good clinical judgment. Additionally, that a majority of patients (79%) had at least some documentation of testosterone levels before initiating therapy implies that most providers are aware of a need to check testosterone levels before starting therapy. However, further education may be needed to help providers understand the need for two low levels checked in the morning and other guideline-recommended practices.

In our study we found that only a small proportion of men with known diseases of the testis, pituitary, and hypothalamus (16%) received testosterone therapy. At least two explanations are plausible. First, the provider may have correctly determined that in spite of the presence of any of these conditions, the patient did not need therapy. For example, not all men with Klinefelter's syndrome or hemochromatosis may require testosterone. The second plausible explanation is that the patient was not treated with therapy in spite of the presence of testosterone deficiency associated with a known condition, reinforcing the suspicion that androgen deficiency is both under- and over-treated.

Our study has important strengths and some limitations. We used a large and highly detailed data set from the nation's largest integrated system of care and adjusted for a comprehensive set of patient-level predictors of testosterone receipt. However, this data set does not permit an evaluation of how patients or providers attach meaning to their health complaints or chronic conditions and whether or how these values influence testosterone prescribing practices. We plan to study patient and provider perceptions toward this therapy in a future qualitative study. Second, although ICD-9 codes are commonly used to identify conditions, these codes may not always be applied accurately by practicing clinicians. We addressed this concern in part by requiring two ICD-9 codes to confirm the conditions. Third, it is possible that the determinants of testosterone prescribing outside the VA may differ from those within the VA, although we suspect that these differences would likely be minor. Fourth, in this study we did not control for any provider- or site-level factors or variability to account for difference in patient populations in these sites in generating the patient-level models. Finally, this analysis focused on predictors of receiving testosterone at least once, i.e., on the factors that motivated the decision to begin therapy. We did not investigate whether patients continue their therapy, and for how long.

The increasing off-label use of testosterone motivated the FDA's recent move to more explicitly restrict the label to diseases of the testis, pituitary, and hypothalamus.[37] Nevertheless, our study suggests that only a small proportion of testosterone prescriptions in the VA (6.3%) are associated with conditions for which testosterone has been approved or for conditions in which individualized testosterone use might be considered reasonable (e.g., opioid or glucocorticoid use). These findings underscore the need for systematic efforts to

optimize testosterone-prescribing practices. A greater understanding of the context within which testosterone is prescribed will facilitate the design of effective quality improvement measures to optimize testosterone prescribing.

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