CLINICAL RESEARCH STUDY

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Elucidating Risk Factors for Androgen Deficiency Associated with Daily Opioid Use☆

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ABSTRACT

BACKGROUND: Opioids can suppress testosterone in men, which can lead to extensive morbidity. Identifying risk factors for androgen deficiency in men using daily opioids could improve monitoring and safety.
METHODS: In a retrospective cohort study, we used Kaiser Permanente Northern California databases to identify men on stable doses of opioids. These subjects had no diagnoses of cancer or endocrine disorders except treated primary hypothyroidism. Subjects were divided into those using long-acting opioids and short-acting opioids. Total testosterone was measured in blood drawn in the morning while the subjects were on their regular dose of opioid. The association between opioid duration of action and androgen deficiency, controlling for dose, body mass index, age, diabetes, hyperlipidemia, and hypertension, was assessed using logistic regression.
RESULTS: The study included 1585 men. Men on long-acting opioids were more likely to be androgen deficient than men on short-acting opioids (57% vs 35%, $P < 0.001$; odds ratio [OR] 3.39; 95% confidence interval [CI], 2.39-4.77). As dose increased, the odds of androgen deficiency increased; however, dose was more strongly associated with androgen deficiency in men on short-acting opioids (OR 1.16; 95% CI, 1.09-1.23, for each 10-mg increase in dose) than in men on long-acting opioids (OR 1.01; 95% CI, 1.01-1.02).
CONCLUSION: Use of long-acting opioids is a key risk factor in the development of androgen deficiency. Dose was significantly associated with androgen deficiency, but more so for men on short-acting than on long-acting opioids.
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KEYWORDS: Androgen deficiency; Chronic pain; Hypogonadism; Long-acting opioid; OPIAD; Opioid; Opioid risk; Short-acting opioid; Testosterone

Opioids remain a cornerstone of treatment for many types of pain, including chronic pain and cancer pain. For the last 2 decades, the belief has been that opioids could be used safely and effectively in selected patients with appropriate monitoring for abuse and diversion and minimal monitoring for side effects such as respiratory depression and constipation.

Low testosterone or androgen deficiency is a common consequence of opioid use that has been documented since the 1970s in men on methadone for maintenance therapy.[1,2] More recently, it has been documented that opioid use is associated with androgen deficiency in men with chronic pain,[3,4] although factors contributing to this deficiency have not been elucidated. In our recent cohort study of 81 men from a chronic pain clinic within Kaiser Permanente Northern California (KPNC), we found that, controlling for morphine standardized equivalent dose (MSE), long-acting opioids were associated with significantly higher odds of androgen deficiency than were short-acting opioids (odds ratio [OR] 4.78; 95% confidence interval, 1.51-15.07).[5]

Androgen deficiency has serious and expensive health consequences. It can cause muscle loss, fatigue, loss of libido, and erectile dysfunction and can lead to decreased bone density, osteoporosis, and increased fracture risk.[6-8] Additionally, androgen deficiency may be involved in the

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development of cardiovascular disease.[9] Thus, androgen deficiency may result in increased risk to patients, decreased quality of life, and potentially increased use of resources to treat sequelae.

The goal of this larger study of a predominately primary care population of men on opioids was to further examine the association between the duration of action of opioids and the risk of development of androgen deficiency.

CLINICAL SIGNIFICANCE

- Long-acting opioids are associated with significantly more risk of androgen deficiency in men than equivalent doses of short-acting opioids.
- Higher opioid dose is associated with increased androgen deficiency, but more so for short-acting opioids than for long-acting opioids.
- These findings hold true when controlling for markers of metabolic syndrome.

METHODS

This retrospective cohort study of 1585 men was conducted within KPNC, a large integrated health care delivery system providing care for more than 3.2 million members in San Francisco and the surrounding Bay Area. Electronic data on demographics, outpatient and inpatient diagnoses and procedures, and pharmacy and laboratory utilization were collected for all study subjects. The Kaiser Foundation Research Institute's Institutional Review Board approved this study with waiver of consent.

Study subjects were men ages 18 to 80 years with at least one total testosterone level measurement performed from January 1, 2007 to December 31, 2011 and who had been dispensed opioid prescriptions demonstrating continuous opioid use. For this study, continuous opioid use was defined as having an opioid possession rate of 90 days' supply during the 100 days before the date on which serum total testosterone was measured. The study index date was the date of the blood draw for serum total testosterone measurement.

Opioids and Duration of Action

For the purposes of this study, opioids were defined as either long acting or short acting. Long-acting opioids were those formulated to provide at least 8 hours of analgesia; some long-acting opioids such as methadone are inherently long acting, whereas others are formulated as controlled-release (CR) or sustained-release (SR) versions of short-acting opioids. The fentanyl patch was considered a long-acting opioid. Short-acting opioids were defined as immediate-release medications providing analgesia for 6 hours or less.[5]

Subjects taking more than 2 different opioids in the study period were excluded, as we did not consider them to be on a stable opioid regimen during the study time frame. Subjects included in the study were taking opioids prescribed in one of 2 possible patterns:

1. Subjects were taking exactly one of the following opioids: codeine; hydrocodone; hydromorphone; fentanyl; methadone; long-acting morphine in the form of either morphine CR or morphine SR; or oxycodone in either a long-acting formulation (oxycodone SR) or a short-acting, immediate-release formulation (oxycodone IR).
2. Subjects were taking exactly one long-acting opioid (fentanyl, methadone, morphine CR or SR, or oxycodone SR) plus exactly one short-acting opioid (codeine, hydrocodone, hydromorphone, or oxycodone IR).

From our clinical experience, we assumed that subjects taking one long-acting opioid plus one short-acting opioid were taking the short-acting opioid for breakthrough pain.

Subjects taking buprenorphine, tramadol, or propoxyphene during the study period were excluded either due to inability to accurately calculate MSE or because they were used for reasons other than chronic pain, such as chemical dependency. Subjects having ambulatory pharmacy records of steroid, supplemental testosterone, or androgen use in the 3 years before measurement of testosterone were excluded from the study. Furthermore, subjects with an inpatient or outpatient diagnosis of any the following conditions in the 3 years before the testosterone measurement also were excluded: pituitary abnormalities, sarcoidosis, Kallmann syndrome, histiocytosis, Klinefelter syndrome, hemochromatosis, malignant neoplasm, or renal disease.

Men were classified as being on short-acting opioids if they were on exactly one short-acting opioid. Men were classified as being on long-acting opioids if they were on either exactly one long-acting opioid or one long-acting opioid and one short-acting opioid. Androgen deficiency was defined as total testosterone <250 ng/dL in a blood sample drawn before 10 AM. The upper limit of 250 ng/dL was chosen based upon the specific assay used within KPNC. Total testosterone, rather than free and total testosterone, was chosen based upon KPNC endocrinology guidelines and the recommendations of the Endocrine Society.[10] Laboratory evaluations of total testosterone were determined using a Siemens Immulite 2000 (Siemens, Munich, Germany) testosterone assay (coefficient of variation 9.6% at 149 ng/dL and 11.1% at 521 ng/dL).

Calculation of MSE

Daily dose for a single purchased opioid was calculated and converted to an MSE using the following formula:[11]

$$\begin{aligned} MSE = &(Opioid\ strength) \times (Number\ of\ pills\ per\ dose) \\ &\times (Number\ of\ doses\ daily) \\ &\times (Morphine\ standardized\ equivalent\ coefficient) \end{aligned}$$

The MSE for subjects on short-acting medications was defined as the MSE corresponding to the opioid purchased

immediately before the index date. If the dispensed quantity was <25% of the dispensed quantity of the previous prescription, then the MSE associated with the larger dispensed quantity was considered to be the MSE. The rationale for this choice was that this change in dose was probably a short-term additional prescription for acute pain to be used on top of the baseline dose rather than a sudden decrease in the chronic dose. Charts of subjects on only long-acting medications were abstracted by hand. For patients on both long- and short-acting opioids, the MSE equal to the most recently purchased long-acting opioid was added to the MSE corresponding to the most recently purchased short-acting opioid. Medical record review was performed on 232 subjects (14.6%) to verify MSE calculations.

Comorbidities

The constellation of conditions that make up metabolic syndrome have been shown to be associated with androgen deficiency.[12-15] Four of the conditions associated with metabolic syndrome were included in our study as potential confounders: diabetes, hyperlipidemia, hypertension, and obesity. Evidence of metabolic syndrome-associated confounders was extracted for each study subject. Subjects with a record of diabetes in the KPNC Division of Research Diabetes Registry[16] at any point before the index date were counted as diabetics. The KPNC Chronic Conditions Management databases were used to identify hypertension in the calendar year before the index date. Subjects having inpatient or outpatient diagnoses indicating hyperlipidemia in the year before index date were considered to have hyperlipidemia. The most recent body mass index (BMI) in the 180 days before the index date was collected; obesity was defined as BMI ≥30.[17] Subjects having any statins dispensed in the outpatient setting in the year before the index date were considered statin users.

Statistical Methods

Univariate summary values for categorical variables are reported as frequencies and proportions and for continuous variables as medians with interquartile ranges (IQRs, 25th and 75th percentile). Bivariate analyses of binomial variables were performed using the chi-squared test. Bivariate analyses of the continuous variables MSE and age were performed using the Wilcoxon-Mann-Whitney nonparametric test. Multivariable analyses were performed using logistic regression. The product of the independent variables duration of action and MSE was added to the logistic regression model to test for interaction.

RESULTS

Patient Characteristics

There were 1585 men who met the inclusion criteria for the study; 616 chronically used long-acting opioids in the 90 days before testosterone was measured, and 969 used short-acting opioids (Table 1). In a bivariate analysis, men who used long-acting opioids were more likely to be androgen deficient (n = 351, 57.0%) than men on short-acting opioids (n = 340, 35.1%, $P < .001$; Table 2). Men with diabetes, hypertension, or hyperlipidemia; taking statins; or with a BMI ≥30 were more likely to have androgen deficiency than men without these conditions (Table 2).

The median MSE for androgen-deficient men was 60 mg (IQR 30-165); the median MSE for men who were not androgen deficient was 40 mg (IQR 20-70, $P < .001$). Age as a continuous variable was not significantly different between androgen-deficient men (median 54 [IQR 47−61]) and men who were not androgen deficient (median 54 [IQR 46−61], $P = .11$).

Duration of Action

Preliminary analyses of our dataset showed that diabetes, hyperlipidemia, hypertension, and age were highly correlated with each other. To avoid multicollinearity in the multivariable analyses, we created a combined variable summarizing all 4 of these patient characteristics. Each subject was given a count of metabolic syndrome–associated conditions (diabetes, hyperlipidemia, and hypertension) combined with age categorized as <50 or ≥50 years. Statin use was not included as an independent variable in our multivariable models because it was too highly correlated with diabetes, hyperlipidemia, and hypertension. In a logistic regression analysis, subjects on long-acting opioids had 3.39 times the odds of having androgen deficiency than patients exclusively on short-acting opioids after controlling for MSE, obesity, and a count of the conditions associated with metabolic syndrome (diabetes, hyperlipidemia, and hypertension) stratified by age (95% confidence interval, 2.39-4.77; Table 3).

Dose

In preliminary analyses, duration of action and dose showed significant interaction. The risk associated with dose was therefore reported for each level of MSE, holding duration of action constant (Table 3). Dose had a greater effect in

Table 1 Population Characteristics by Study Group

Characteristic	Short-acting Opioids n = 969	Long-acting Opioids n = 616
Age, median (IQR)	54 (46-61)	54 (46.5-61)
Dose, median (IQR)	30 (20-40)	150 (90-251.25)
Obese,* n (%)	257 (42.6%)	440 (46.8%)
Diabetes, n (%)	172 (17.8%)	107 (17.4%)
Hypertension, n (%)	362 (58.8%)	574 (59.2%)
Hyperlipidemia, n (%)	393 (40.6%)	210 (34.1%)
Statin use, n (%)	351 (36.2%)	201 (32.6%)

IQR = interquartile range.
*Body mass index data on 42 subjects missing.

Table 2 Unadjusted Rates of Androgen Deficiency According to Patient Risk Factors

	Not Androgen Deficient	Androgen Deficient (Total Testosterone ≤ 250 ng/dL)	*P* Value*
Duration of action of opioid			
Long (n = 616)	265 (43.0%)	351 (57.0%)	<.001
Short (n = 969)	629 (64.9%)	340 (35.1%)	
Obese†			
Obese	318 (45.6%)	379 (54.4%)	<.001
Not obese	551 (65.1%)	295 (34.9%)	
Diabetes			
Diabetes	125 (44.8%)	154 (55.2%)	<.001
No diabetes	769 (58.9%)	537 (41.1%)	
Hypertension			
Hypertension	481 (51.4%)	455 (48.6%)	<.001
No hypertension	413 (63.6%)	236 (36.4%)	
Hyperlipidemia			
Hyperlipidemia	310 (51.4%)	293 (48.6%)	.002
No hyperlipidemia	584 (59.5%)	398 (40.5%)	
Statins			
Statins use	256 (46.4%)	296 (53.6%)	<.001
No statins use	638 (61.8%)	395 (38.2%)	

*Chi-squared test.
†Body mass index values were missing for 42 subjects.

men taking short-acting opioids (increase in the OR for androgen deficiency of 1.16 for every 10-mg increase in MSE) than in men taking long-acting opioids (increase in the OR of 1.01 for every 10-mg increase in MSE). Having 2 or 3 metabolic syndrome-associated conditions and age ≥50 years also increased the OR for androgen deficiency (Table 3).

Low-risk Patients

We also performed a logistic regression assessing risk of androgen deficiency among 304 subjects having a BMI <30, no diabetes, no hypertension, and no hyperlipidemia (Table 4). Among these men, subjects on long-acting opioids had odds of androgen deficiency 5.78 times that of subjects on short-acting opioids. However, subjects on short-acting opioids had 24% greater odds of androgen deficiency for every 10-mg increase in MSE, as compared with 2% greater odds in subjects taking long-acting opioids.

DISCUSSION

The finding that duration of action is inversely related to testosterone levels in men on opioids initially seems counterintuitive. The standard approach to opioid management has long focused on switching patients who use opioids daily to a long-acting formulation to achieve more stable blood levels of drug and therefore, in theory, better pain control.[18,19] There is, however, no evidence that long-acting opioids are either more efficacious or safer than their short-acting counterparts.[20-24]

Sustained serum drug levels may be responsible for the increased incidence of androgen deficiency in men on long-acting opioids. Because testosterone is produced in men in response to pulsatile secretion of gonadotropin-releasing hormone (GnRH) and then luteinizing hormone (LH), it is possible that a serum drug level exists above

Table 3 Adjusted Odds Ratios for Androgen Deficiency*

	Odds Ratio	95% Confidence Interval
Duration of action		
Long (vs short)	3.39	2.39-4.77
Dose (MSE)		
Total MSE (10 mg) duration = short	1.16	1.09-1.23
Total MSE (10 mg) duration = long	1.01	1.01-1.02
Obese		
Obese vs not obese	2.22	1.78-2.77
Missing vs not obese	1.51	0.77-2.89
Number of conditions by age†		
(referent: 0 conditions, <50 years old)		
0 conditions, ≥50	0.91	0.60-1.36
1 condition, <50	1.50	1.00-2.26
1 condition, ≥50	1.34	0.95-1.90
2 conditions, <50	1.43	0.81-2.51
2 conditions, ≥50	1.95	1.36-2.79
3 conditions, <50	1.21	0.52-2.77
3 conditions, ≥50	2.59	1.64-4.12

MSE = morphine standardized equivalent dose.
*The model was adjusted for MSE, obesity, and a count of the following conditions stratified by age: diabetes, hyperlipidemia, and hypertension.
†The number of conditions is a count of the number of comorbidities present (diabetes, hypertension, hyperlipidemia) stratified by age < 50 and age >50 years.

Table 4 Adjusted Odds Ratios for Androgen Deficiency in Patients with BMI <30, No Diabetes, No Hypertension, and No Hyperlipidemia

	Odds Ratio	Confidence Interval
Duration of action		
Long (vs short)	5.78	2.44-13.67
Dose		
10-mg increase, short duration	1.24	1.07-1.44
10-mg increase, long duration	1.02	1.00-1.03
Age (in years)	1.01	0.99-1.04

BMI = body mass index.

which these pulses are less frequent or the amplitude of these pulses is inadequate to maintain normal testosterone levels. By contrast, short-acting opioids have serum drug levels that may rise and fall several times a day. It may be that short-acting opioids halt normal testosterone production during peak levels, but there is sufficient "trough" time during each day to allow some GnRH-LH-testosterone cycles to complete and thereby to maintain testosterone levels above our threshold of 250 ng/dL. We name this concept the "nadir hypothesis": the idea that stable serum drug levels may prevent normal endocrine function and that intermittent nadirs in drug levels allow testosterone to be produced normally, at least during these nadirs. Supporting this idea, a single MSE of morphine suppresses gonadal function in rats for a period of about 4 hours, roughly equivalent to one half-life of the drug.[25] If morphine were dosed every 6 hours, then there might well be a recovery of testosterone production between hours 4 and 6 that would allow levels to return to normal. Intermittent testosterone production may be adequate to maintain normal total testosterone levels in men. Our finding that each 10-mg increase in MSE among subjects using exclusively short-acting opioids was associated with a higher odds of androgen deficiency than the odds associated with each 10-mg increase in MSE among subjects using long-acting opioids provides additional support for this hypothesis. As the MSE of a short-acting opioid increases, there may be less time during a 24-hour period when nadir serum levels are reached, either because doses are taken at closer and closer intervals until they basically approach continuous delivery or because the higher doses produce higher peaks in serum levels, leaving less time to reach an adequate nadir before the next dose is consumed. If short-acting opioids are consumed before drug levels from the prior dose have fallen, the short-acting opioid in effect mimics a long-acting opioid. The fentanyl patch is a perfect example of this: it is a very short-acting opioid with near-continuous delivery in patch form that makes the drug perform like a long-acting opioid, providing stable rather than fluctuating drug levels.

In this large cohort of men on chronic daily opioid therapy for chronic pain, we have shown that long-acting opioids are associated with a greater odds ratio of androgen deficiency than equivalent doses of short-acting opioids. Additionally, we were able to examine the effects of several other comorbidities that are associated with androgen deficiency, including hyperlipidemia, hypertension, and diabetes,[15] but it is not known whether these morbidities are causative. Indeed, recent investigations point to a bidirectional relationship, whereby androgen deficiency levels lead to higher sugars, lipids, and blood pressure in men, and these comorbidities in turn lower testosterone.[9,26] In the current study, when we controlled for these comorbidities, and when we examined a subset of patients without these diagnoses, duration of action remained the most significant contributor to androgen deficiency. Age was not a significant factor when we evaluated men with no metabolic syndrome indicators. Although testosterone can decline with age, many men maintain normal testosterone levels into advanced age.[27] In this population of men on opioids, it is possible that age does not play a significant role or that the effect of the opioids exerts a greater influence on testosterone than age and therefore any influence of age is masked by opioid use.

Recently, the awareness of androgen deficiency in men on opioids has increased. Several studies have shown that this occurs frequently in men who use opioids daily, and this effect can happen quickly and can be profound, although it is usually reversible if the opioid medications are removed.[1,28,29] Because opioids remain a cornerstone in the treatment of many types of pain, elucidating the risks and defining circumstances under which those risks are more likely to occur is crucial.

Strengths and Limitations

The strength of this study is the size, which allowed us to develop a robust model that controlled for the comorbidities that are most commonly associated with androgen deficiency in men.

However, a limitation is that, because testosterone levels are still not routinely tested in the primary care environment, the subjects may have been symptomatic and may have asked for, or been offered, a total testosterone level test; as such, they may not be representative of all patients on daily opioids. However, unlike what we would expect in a primarily symptomatic population, the incidence of androgen deficiency in this study is actually lower than that reported in many previous studies, including our previous study of men seen in a tertiary pain clinic.[4,30-32]

Although opioids have been postulated to affect testosterone at the level of the hypothalamus (GnRH),[33] the pituitary (LH),[34,35] and the testes directly,[36] we do not have sufficient evidence from this retrospective study to speculate at which point in the hypothalamic-pituitary-gonadal axis opioids are affecting testosterone levels.

We also did not look at race in this study. Although the incidence of prostate cancer is higher in African American populations, in at least one study there was no difference in

incidence of androgen deficiency between races.[37] We also did not look at depression, which has been linked to androgen deficiency in men, although, as with metabolic syndrome, the direction of this relationship is unknown. The link between depression and androgen deficiency should be investigated further.

As in any retrospective study, we cannot be sure that the subjects were taking their medications as prescribed. Because KPNC is a closed system and all patients in this study received their medications from our pharmacy, we can calculate the possession rate (days of medication dispensed based on the medication instructions vs days between refills) as a proxy for MSE. Also, because opioids are dependence forming, most patients on these medications do take them every day and at regular intervals. Finally, although we excluded patients with cancer diagnoses from our cohort, we cannot be sure that all men in this cohort were taking opioids for noncancer pain.

CONCLUSION

In a large retrospective study of 1585 men taking opioids daily for noncancer pain, the duration of action was strongly associated with androgen deficiency even when accounting for or eliminating comorbidities such as obesity, diabetes, hypertension, and hyperlipidemia. MSE does play a role but seems to be more strongly associated with androgen deficiency among men who use exclusively short-acting opioids. Future prospective studies are needed to further elucidate the relationship between duration of action and androgen deficiency and to clearly identify the mechanism involved.

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References

1. Azizi F, Vagenakis AG, Longcope C, et al. Decreased serum testosterone concentration in male heroin and methadone addicts. *Steroids*. 1973;22:467-472.
2. Cicero TJ, Bell RD, Wiest WG, et al. Function of the male sex organs in heroin and methadone users. *N Engl J Med*. 1975;292:882-887.
3. Smith HS, Elliott JA. Opioid-induced androgen deficiency (OPIAD). *Pain Physician*. 2012;15:ES145-ES156.
4. Fraser LA, Morrison D, Morley-Forster P, et al. Oral opioids for chronic non-cancer pain: higher prevalence of hypogonadism in men than in women. *Exp Clin Endocrinol Diabetes*. 2009;117:38-43.
5. Rubinstein AL, Carpenter DM, Minkoff JR. Hypogonadism in men with chronic pain linked to the use of long-acting rather than short-acting opioids. *Clin J Pain*. 2013;29:840-845.
6. Mattia C, Di Bussolo E, Coluzzi F. Non-analgesic effects of opioids: the interaction of opioids with bone and joints. *Curr Pharm Des*. 2012;18:6005-6009.
7. Daniell HW. Opioid osteoporosis. *Arch Intern Med*. 2004;164:338; author reply, 338.
8. Tuck SP, Francis RM. Testosterone, bone and osteoporosis. *Front Horm Res*. 2009;37:123-132.
9. Kelly DM, Jones TH. Testosterone: a vascular hormone in health and disease. *J Endocrinol*. 2013;217:R47-R71.
10. 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.
11. Pereira J, Lawlor P, Vigano A, et al. Equianalgesic dose ratios for opioids. a critical review and proposals for long-term dosing. *J Pain Symptom Manage*. 2001;22:672-687.
12. Jones TH. Effects of testosterone on Type 2 diabetes and components of the metabolic syndrome. *J Diabetes*. 2010;2:146-156.
13. Kang HY. Beyond the male sex hormone: deciphering the metabolic and vascular actions of testosterone. *J Endocrinol*. 2013;217:C1-C3.
14. Muraleedharan V, Jones TH. Testosterone and the metabolic syndrome. *Ther Adv Endocrinol Metab*. 2010;1:207-223.
15. Rao PM, Kelly DM, Jones TH. Testosterone and insulin resistance in the metabolic syndrome and T2DM in men. *Nat Rev Endocrinol*. 2013;9:479-493.
16. Moffet HH, Adler N, Schillinger D, et al. Cohort profile: the Diabetes Study of Northern California (DISTANCE)—objectives and design of a survey follow-up study of social health disparities in a managed care population. *Int J Epidemiol*. 2009;38:38-47.
17. Kuczmarski RJ, Carroll MD, Flegal KM, Troiano RP. Varying body mass index cutoff points to describe overweight prevalence among U.S. adults: NHANES III (1988 to 1994). *Obes Res*. 1997;5:542-548.
18. *VA/DoD Clinical Practice Guideline for the Management of Opioid Therapy for Chronic Pain*. Washington, DC: Department of Veteran Affairs; May 2010. Available at: http://www.healthquality.va.gov/guidelines/Pain/cot/COT_312_Full-er.pdf. Accessed October 9, 2014.
19. Mendelson JH, Mendelson JE, Patch VD. Plasma testosterone levels in heroin addiction and during methadone maintenance. *J Pharmacol Exp Ther*. 1975;192:211-217.
20. Argoff CE, Silvershein DI. A comparison of long- and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. *Mayo Clin Proc*. 2009;84:602-612.
21. Wilsey BL, Fishman S, Li CS, et al. Markers of abuse liability of short- vs long-acting opioids in chronic pain patients: a randomized crossover trial. *Pharmacol Biochem Behav*. 2009;94:98-107.
22. Stambaugh JE, Reder RF, Stambaugh MD, et al. Double-blind, randomized comparison of the analgesic and pharmacokinetic profiles of controlled- and immediate-release oral oxycodone in cancer pain patients. *J Clin Pharmacol*. 2001;41:500-506.
23. Grosset AB, Roberts MS, Woodson ME, et al. Comparative efficacy of oral extended-release hydromorphone and immediate-release hydromorphone in patients with persistent moderate to severe pain: two randomized controlled trials. *J Pain Symptom Manage*. 2005;29:584-594.
24. Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. *Clin J Pain*. 1999;15:179-183.
25. Ceccarelli I, De Padova AM, Fiorenzani P, et al. Single opioid administration modifies gonadal steroids in both the CNS and plasma of male rats. *Neuroscience*. 2006;140:929-937.
26. Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. *J Endocrinol*. 2013;217:R25-R45.
27. 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.

28. Woody G, McLellan AT, O'Brien C, et al. Hormone secretion in methadone-dependent and abstinent patients. *NIDA Res Monogr*. 1988;81:216-223.
29. Mendelson JH, Meyer RE, Ellingboe J, et al. Effects of heroin and methadone on plasma cortisol and testosterone. *J Pharmacol Exp Ther*. 1975;195:296-302.
30. Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab*. 2000;85:2215-2222.
31. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Hypogonadism and sexual dysfunction in male cancer survivors receiving chronic opioid therapy. *J Pain Symptom Manage*. 2003;26:1055-1061.
32. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. *J Pain*. 2002;3:377-384.
33. Orstead KM, Spies HG. Inhibition of hypothalamic gonadotropin-releasing hormone release by endogenous opioid peptides in the female rabbit. *Neuroendocrinology*. 1987;46:14-23.
34. Xenidis M, Pandya N, Hames E. Effects of intrathecal opioid administration on pituitary function. *Pain Med*. 2013;14:1741-1744.
35. Wylot B, Tworus K, Okrasa S. The effects of mu-, delta- and kappa-opioid receptor activation on luteinizing and follicle-stimulating hormone secretion from porcine pituitary cells. *J Physiol Pharmacol*. 2013;64:505-511.
36. Adams ML, Sewing B, Forman JB, et al. Opioid-induced suppression of rat testicular function. *J Pharmacol Exp Ther*. 1993;266:323-328.
37. Mulligan T, Frick MF, Zuraw QC, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006;60:762-769.