Hypogonadism in Men With Chronic Pain Linked to the Use of Long-acting Rather Than Short-acting Opioids

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Aim: There is a need to elucidate the variables associated with testosterone suppression among men on daily opioid therapy for chronic pain.

Objective: The objective of this study was to examine several variables related to opioid use including daily dose, duration of action (long acting vs. short acting), and specific opioid to ascertain specific influences on total serum testosterone levels in men with chronic pain who use opioids daily.

Setting: This is a retrospective cohort study of men within the Kaiser Permanente, Northern California (KPNC) health care system on some form of daily opioid use for chronic pain.

Participants: Eighty-one men between the age of 26 and 79 years were seen in a chronic pain clinic between January 2009 and June 2010. All men were on stable dose of an opioid for at least 3 months, none with a previous diagnosis of hypogonadism.

Main Outcome Measures: Total serum AM testosterone levels were measured at KPNC Regional Laboratory.

Results: Average total serum AM testosterone levels for this population showed 34% of all men receiving daily opioids were hypogonadal (AM total serum testosterone <250 ng/dL). In men receiving long-acting opioids, 74% (34/46) were hypogonadal compared with 34% (12/35) in men using short-acting opioids (hydrocodone or oxycodone) exclusively [AM total testosterone: median, 126 ng/dL; mean, 169 ng/dL (SD, 128 ng/dL)] vs. median, 283 ng/dL; mean, 315 ng/dL (SD, 142 ng/dL); P < 0.001]. After controlling for daily dosage and body mass index, men on long-acting opioids had 4.78 times greater odds of becoming hypogonadal than did men on short-acting opioids [95% confidence interval (CI), 1.51-15.07; P = 0.008]. Body mass index was also significantly associated with hypogonadism (odds ratio, 1.13; 95% CI, 1.03-1.24; P = 0.006), whereas daily dose was not (odds ratio, 1.02; 95% CI, 0.99-1.05; P = 0.29).

Conclusions: Among a contemporary sample of men receiving chronic daily opioids, we found a high prevalence of hypogonadism associated with duration of action, but not with total daily dose of the opioid.

Key Words: opioid, chronic pain, long-acting opioid, short-acting opioid, hypogonadism, testosterone, opioid risk

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PATIENTS AND METHODS

Study Population

This was a retrospective cohort study of men between the age of 18 and 80 years referred to the Santa Rosa Chronic Pain Clinic within Kaiser Permanente, Northern California (KPNC) for evaluation between January 2009 and June 2010. All men carried a diagnosis of chronic pain, defined as pain lasting more than 3 months without any etiology that allowed for a definitive or curative treatment. Chronic pain conditions in this cohort consisted primarily...
of low back pain and myofascial pain but also included failed back syndrome, spinal stenosis, chronic headaches, peripheral neuropathy, rheumatoid arthritis, and ankylosing spondylitis. Men with previously diagnosed hypogonadism, a history of prostate cancer, or those with a known endocrine disorder, aside from stable, treated hypothyroidism, were excluded. All men were on a stable dose of daily opioid defined as an unchanged opioid dose with at least 3 prescriptions of 30-day supply purchased at a KPNC pharmacy in the preceding 100 days. A urine toxicology screen to ensure compliance with pain medications and an AM serum total testosterone level (TT) were obtained in all men, as is our usual practice.

Of 91 men tested, 3 men receiving intrathecal opioids were excluded because of an inability to reliably calculate a 24-hour morphine-standardized equivalent dose (MSE) for them; of these 3 men 2 had TT levels < 250 ng/dL. Also excluded was 1 patient who admitted to using opioids that were not being prescribed for him which made it impossible to calculate his daily MSE. There were 5 men on “rare” opioids who were also excluded from analysis. A rare opioid in this case was defined as a drug or formulation that was being used by only 1 person in the study. It was felt that anonymity could not be assured for these patients if they were included in the results. One man with low TT was found to have hypogonadism based on primary gonadal failure, and he was also eliminated from analysis. The total number of men included in this analysis was 81. Electronic data maintained in KPNC databases on outpatient and inpatient diagnoses and procedures as well as ambulatory pharmacy and laboratory utilization were collected on all study patients.

All patients with a low TT level were offered a complete endocrine evaluation to exclude other causes of hypogonadism. The endocrine evaluation included electrolytes, renal function, liver function creatinine, lipids, follicle stimulating hormone, luteinizing hormone (LH), prostate specific antigen, thyroid stimulating hormone, thyroxine (T4), iron, total iron binding capacity, prolactin, a repeat TT, bone densitometry, and an MRI of the pituitary.

All laboratory studies were performed at the KPNC Regional Laboratory in Richmond, California. All laboratory tests and studies were performed as standard practices in coordination with our Department of Endocrinology. The KPNC Region Institutional Review Board approved this study with waiver of signed consent.

Baseline Characteristics

For each patient, the characteristics collected included age, body mass index (BMI (kg/m²))³⁸, specific opioid therapy, total daily MSE, and duration of action. The total daily MSE was calculated using the globaliph.com algorithm as well as methods previously described by Pereira et al.¹⁹ TT levels were obtained on each man as is recommended by the Endocrine Society.²⁰²¹ Hypogonadism was defined for all men as a TT level ≤ 250 ng/dL. All laboratory measurements were obtained before 10 AM.

For the purpose of this study, opioids were defined as either LAO or short-acting opioid (SAO) based on their duration of action. LAOs are generally formulated to behave like LAOs. The fentanyl patch was included as an LAO due to its formulation, which allows it to provide 72 hours of constant drug delivery per patch. SAOs by contrast are characterized by a rapid increase and decrease in serum levels and a duration of analgesia of < 6 hours.

Men who were on both an LAO and an SAO were included in the LAO group only and their total daily MSE was calculated based upon both medications. Men who were on 2 different opioids that were both short acting were included in the specific drug group corresponding to the larger dose; their total daily MSE was calculated based on the MSE of both of their SAOs. No men in this study were on 2 different LAOs.

Buprenorphine

Eight patients in our cohort were on sublingual buprenorphine, which is currently approved for treatment of chemical dependency. All of these patients had chronic pain and were opioid dependant before placement on buprenorphine. In all cases either the patient self-identified a concern with opioid use, or a decision between patient and physician was made that buprenorphine would be an appropriate choice given the patient’s use patterns, which included escalating opioid doses, inability to control their use, or rapidly decreasing efficacy of opioid medications. Although these patients meet the criteria for chemical dependency, this medication also provides highly effective analgesia.

Laboratory Evaluations

TT was determined using Siemens Immulite 2000 Testosterone assay. (CV 9.6% at 149 ng/dL and 11.1% at 521 ng/dL).

Statistical Analyses

The association between hypogonadism and the duration of action of opioid as well as the potential confounders age, BMI, and MSE was evaluated. We performed univariate, bivariate, and multivariable analyses. Univariate analyses were performed to assess the distribution of the variables. We then performed bivariate analyses to assess the association between hypogonadism and opioid duration of action. Bivariate analyses were also performed to evaluate the association between the potential confounders age, BMI, MSE, and hypogonadism, as well as opioid duration of action. We performed multivariable analyses to assess the association between opioid duration of action and hypogonadism controlling for age, BMI, and MSE.

Bivariate analysis of the dichotomous variable duration of action was performed using the χ² test. Bivariate analyses of continuous variables were performed using the Wilcoxon-Mann-Whitney nonparametric test, as the values for age, BMI, and MSE were found to be not normally distributed. The association of duration of action of opioids with hypogonadism controlling for age, BMI, and MSE was evaluated with logistic regression. There was inadequate power to assess the association between specific opioids and hypogonadism in this study. Data management and statistical analyses were performed using SAS version 9.13 (SAS Institute Inc., Cary, NC).

RESULTS

The study population consisted of a total of 81 patients who were between the age of 26 and 79 years (median/mean age, 51 y) at the time of their first visit to our
TABLE 1. Characteristics of Hypogonadal and Nonhypogonadal Men With Long-term use of Opioids

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Duration of Action</th>
<th>Median</th>
<th>Mean</th>
<th>No. Patients (% of Total)</th>
<th>No. Hypogonadal (% Hypogonadal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>LAO</td>
<td>286</td>
<td>256</td>
<td>8 (9.9%)</td>
<td>3 (37.5%)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>LAO</td>
<td>129</td>
<td>193</td>
<td>4 (4.9%)</td>
<td>3 (75.0%)</td>
</tr>
<tr>
<td>Methadone</td>
<td>LAO</td>
<td>110</td>
<td>150</td>
<td>14 (17.3%)</td>
<td>11 (78.6%)</td>
</tr>
<tr>
<td>Morphine CR</td>
<td>LAO</td>
<td>127</td>
<td>150</td>
<td>12 (14.8%)</td>
<td>10 (83.3%)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>LAO</td>
<td>109</td>
<td>134</td>
<td>8 (9.9%)</td>
<td>7 (87.5%)</td>
</tr>
<tr>
<td>Oxycodone IR</td>
<td>SAO</td>
<td>237</td>
<td>286</td>
<td>10 (12.3%)</td>
<td>5 (50.0%)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>SAO</td>
<td>293</td>
<td>326</td>
<td>25 (30.9%)</td>
<td>7 (28.0%)</td>
</tr>
</tbody>
</table>

CR indicates controlled-release; IR, immediate-release; LAO, long-acting opioids; SAO, short-acting opioids; TT, serum AM total testosterone.

DISCUSSION

Although this cohort study confirms a 74% incidence of hypogonadism for men on LAOs, the incidence of hypogonadism is significantly lower (34%) for men maintained on SAOs. The distribution of daily MSE differs according to duration of action. Patients on SAOs were generally on lower doses, <100 mg of MSE daily. This may be due to the dose-limiting acetaminophen contained in the most commonly prescribed SAOs containing hydrocodone and oxycodone. The men on LAOs by contrast had no dose-limiting constraints. In our clinical experience, men on LAOs tend to escalate their MSE over time, possibly due to increased medication tolerance. It may be also that pain thresholds drop and opioids are less effective in the context of low testosterone.22 In this study it was imperative to control for total daily MSE when assessing the association between duration of action and hypogonadism in our logistic regression. We found that duration of action was associated with hypogonadism, and MSE was not; additional studies on larger sample sizes are needed to further assess this relationship.

Animal studies have shown that opioids exert their effect on the testosterone primarily through inhibition of chronic pain department. The median BMI of this population was 29 kg/m² and the mean was 31 kg/m².

Forty-six patients (56.8%) were determined to be hypogonadal, and 35 (43.2%) were not. The characteristics of hypogonadal and nonhypogonadal men are described in Table 1. Hypogonadal men had a higher median BMI than nonhypogonadal men (P < 0.001). There was no significant difference in age between the 2 groups. Men who were hypogonadal were on a higher median MSE of opioid (median, 105 mg/mean, 259 mg) than men who were not hypogonadal (median, 30 mg/mean, 86 mg; P < 0.001). Opioids by duration of action as well as percentage of hypogonadal patients by opioid regimens are described in Table 2.

A significantly higher proportion of men on LAOs (34/46, 74%) were hypogonadal compared with those on SAOs (12/35, 34%, P < 0.001). Characteristics of study patients by duration of action of opioid are shown in Table 3. There were no significant differences in age or BMI between the 2 groups. Patients on SAOs had a lower median and mean MSE (median MSE, 30 mg; mean MSE, 40 mg) than those on LAOs (median MSE, 135 mg; mean MSE, 295 mg; P < 0.001). Men on SAOs had a higher median and mean TT level than men on LAOs (SAO: median, 283 ng/dL; mean, 315 ng/dL vs. LAO: median, 126 ng/dL; mean, 169 ng/dL; P < 0.001). The association of duration of action with hypogonadism controlling for MSE and BMI was evaluated using logistic regression (Table 4). When controlling for MSE and BMI, patients on a regimen of LAOs had 4.78 times greater odds of being hypogonadal than did patients on a regimen of SAOs [95% confidence interval (CI), 1.51-15.07; P = 0.008]. The CI for duration of action is wide, but the effect is also large. When controlling for dosage as well as duration of action, BMI was found to be significant. For every unit increase of BMI, patients had an additional 2% greater chance of being hypogonadal. MSE, however, was not significantly associated with hypogonadism (95% CI, 0.99-1.05; P = 0.29). Age was not significantly associated with hypogonadism in the bivariate analyses and was therefore not included as a dependent variable in the logistic regression.

The possibility of duration of action affecting hypogonadism differently depending on dosage was considered. We included the product of duration of action and MSE as an independent variable to assess whether or not duration of action behaves differently as MSE increased. We found that this interaction term was not significantly associated with hypogonadism.
pulsatile GnRH, which leads to loss of pulsatile LH release and in turn lower testosterone. There is a high concordance between pulsatile GnRH and LH secretion. One mechanism that could explain the greater suppressive effects of LAOs compared with SAOs may stem from the relatively more stable serum drug levels achieved with LAOs. There may be a threshold serum drug level that causes GnRH suppression, and both LAOs and SAOs may acutely cause this suppression. With SAO use serum drug levels should vary more throughout a 24-hour cycle. As serum drug levels fall, GnRH suppression may cease leading to LH production and testosterone. This intermittent GnRH and LH suppression may allow enough testosterone to be produced to keep men in the clinically normal range. There are to date no studies that examine this specific mechanism with respect to exogenous opioids of differing durations of action in humans; however, there are some small amounts of supporting data from animal studies. A single-dose morphine has been shown to reduce testosterone levels in rats after 4 hours; this effect is predominately reversed after 24 hours.23 Opioid agonists have been shown to change GnRH and LH levels in humans and animals acutely, and this effect is reversed by administration of the opioid antagonist naloxone.24–27

LAOs have long been believed to offer less risk of abuse because the central effect or “high” that can lead to addictive behaviors is at least in part a result of rapidly changing serum levels rather than the absolute serum concentration. However, there is no evidence of decreased abuse potential with LAO compared with SAO.28,29 Randomized controlled trials comparing efficacy of LAO relative to SAO have also failed to show superiority in terms of pain control.30–33 To our knowledge, our study is the first to examine a risk directly related to the duration of action of a medication. Our results may raise the question of whether the risks associated with LAOs are less favorable than those associated with SAOs. More studies would be required to further elucidate this mechanism.

**TABLE 3. Characteristics by Duration of Action of Opioid**

<table>
<thead>
<tr>
<th>Duration of Action</th>
<th>Median/Mean</th>
<th>N</th>
<th>MSE (mg)</th>
<th>BMI (kg/m²)</th>
<th>Age (y)</th>
<th>TT (ng/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAO</td>
<td></td>
<td>46</td>
<td>135/295</td>
<td>30/30</td>
<td>52/52</td>
<td>126/169</td>
</tr>
<tr>
<td>SAO</td>
<td></td>
<td>35</td>
<td>30/40</td>
<td>28/31</td>
<td>52/53</td>
<td>283/315</td>
</tr>
<tr>
<td><strong>P</strong></td>
<td></td>
<td></td>
<td>&lt; 0.0001</td>
<td>0.65</td>
<td>0.64</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Analyses performed using the Wilcoxon-Mann-Whitney nonparametric test.

BMI indicates body mass index; LAO, long-acting opioids; MSE, morphine-standardized equivalent dose in mg; SAO, short-acting opioids; TT, serum AM total testosterone.

**Buprenorphine**

It should be noted that buprenorphine was counted as an LAO in this study, but previous studies suggest that it is associated with significantly less hypogonadism than methadone.16,17 Thirty-eight percent of men on buprenorphine were found to be hypogonadal, but our sample size was too small to evaluate statistically the association between each drug and hypogonadism. This proportion, however, is consistent with the crude prevalence of hypogonadism in the general population reported in 1 recent study.34 An evaluation with a larger sample size could perhaps clarify the association between risk of hypogonadism and the use of buprenorphine.

**Strengths and Limitations**

A strength of this study was that it was conducted in KPNC, a large integrated health care delivery system providing care for more than 3.2 million members in the San Francisco and greater Bay Area. KPNC’s electronic medical record system and robust laboratory, pharmacy, hospital, and medical office diagnosis databases allow for more complete data capture. Although our cohort size of 81 is small, it is one of the largest reported to date of men receiving chronic, daily opioid therapy. A limitation of our study was that the sample size of our cohort was too small to allow us to assess potential differences in rates of hypogonadism between specific drugs. In addition, the men in this study were all referred to our tertiary pain clinic, presumably for increasing pain, decreasing efficacy of treatment, or general failure to improve, and therefore may not be representative of the population of chronic pain patients in general. The symptoms of hypogonadism including increased pain, depressed mood, and a general decreased response to opioid treatment may have contributed to the referral in the first place.

Although we used urine toxicology screening and pharmacy records to help ensure compliance with the medications being prescribed, we could not guarantee that each man was taking his opioid as prescribed. We have no data on the relationship between time of dosing and time of TT measurement.

Additional variables not evaluated in this study but known to be associated with low testosterone in men include atherosclerosis, metabolic syndrome, dyslipidemia, hypertension, and type 2 diabetes. What is not known, however, is whether these morbidities are contributory to low testosterone levels in men or are a result of low testosterone levels.35–38 Indeed the relationship may be bidirectional, implying both that these diseases contribute to lower testosterone levels in men and that low testosterone

**TABLE 4. Association of Duration of Action With Hypogonadism Controlling for Dosage and BMI**

<table>
<thead>
<tr>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of action</td>
<td>4.78</td>
<td>1.51-15.07</td>
</tr>
<tr>
<td>(LAO vs. SAO)</td>
<td>1.02</td>
<td>0.99-1.05</td>
</tr>
<tr>
<td>MSE</td>
<td>1.13</td>
<td>1.03-1.24</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis performed using logistic regression.

BMI indicates body mass index; LAO, long-acting opioids; MSE, morphine-standardized equivalent dose (mg); SAO, short-acting opioids.
levels may aggravate or contribute to the development of the diseases.

With a sample size of 81 patients it was not possible to include each of these factors in the model. A larger study is needed to further define the relationship between these morbidities and testosterone levels.

**CONCLUSIONS**

LAOs have been the mainstay of opioid treatment for chronic pain for the last decade. It has been estimated that 4.3 million Americans use opioids on a daily basis. To date no study has shown a difference in safety or efficacy between LAOs and SAOs. This is the first study to suggest that independent of MSE, daily use of LAOs is associated with hypogonadism compared with daily use of SAOs. Future studies both prospective and epidemiologic that can control for other causes of hypogonadism are needed to further define the relationship between duration of action and testosterone suppression in men who consume opioids daily for chronic pain.

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