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Prescription Opioids for Back Pain and Use of Medications for Erectile Dysfunction

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Abstract

Study Design—Cross-sectional analysis of electronic medical and pharmacy records.

Objective—To examine associations between use of medication for erectile dysfunction or testosterone replacement and use of opioid therapy, patient age, depression, and smoking status

Summary of Background Data—Men with chronic pain may experience erectile dysfunction related to depression, smoking, age, or opioid-related hypogonadism. The prevalence of this problem in back pain populations and the relative importance of several risk factors are unknown.

Methods—We examined electronic pharmacy and medical records for men with back pain in a large group model HMO during 2004. Relevant prescriptions were considered for six months before and after the index visit.

Results—There were 11,327 men with a diagnosis of back pain. Men who received medications for erectile dysfunction or testosterone replacement (n = 909) were significantly older than those who did not, and had greater comorbidity, depression, smoking, and use of sedative-hypnotic medications. In logistic regressions, long-term opioid use was associated with greater use of medications for erectile dysfunction or testosterone replacement, compared to patients with no opioid use (OR 1.45, 95% CI 1.12, 1.87, p<0.01). Age, comorbidity, depression, and use of sedative-hypnotics were also independently associated with use of medications for erectile dysfunction or testosterone replacement. Patients prescribed daily opioid doses of 120 mg morphine-equivalent or more had greater use of medication for erectile dysfunction or testosterone replacement than patients without opioid use (OR 1.58, 95% CI 1.03, 2.43), even with adjustment for duration of opioid therapy.

Conclusion—Opioid dose and duration, as well as age, comorbidity, depression, and use of sedative-hypnotics were associated with evidence of erectile dysfunction. These findings may be important in the process of decision-making for long-term opioid use.

Keywords

opioids; low back pain; erectile dysfunction; sexual dysfunction

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INTRODUCTION

Opioid use for chronic non-cancer pain, including back pain, is increasingly common,[1–6] but the long-term efficacy and safety of opioids for this purpose remain uncertain.[7] The prevalence and clinical relevance of some consequences of long-term use, such as endocrinologic changes and sexual dysfunction, are still being elucidated.

Sexual dysfunction is often associated with chronic pain[8] and has been associated with opioid use,[9,10] but also with depression, which often accompanies chronic pain.[11] Depressed patients may be more likely to initiate opioid therapy,[12–15] but opioids may also cause or exacerbate depression. Smoking is also associated with both prescription opioid use and erectile dysfunction in men.[16–18] Obesity is associated with both reduced testosterone levels and opioid prescribing and duration.[16,19, 20] Thus, in addition to opioid use, there are multiple factors that may be associated with sexual dysfunction in patients with chronic pain.

Hypogonadism as a result of oral opioid therapy has recently been documented both in men and women,[9,10,21,22] but knowledge gaps persist regarding its prevalence, risk factors, functional significance, and the influence of comorbidity.[23] There is some evidence that hypogonadism is opioid dose-related.[9] There may be multiple mechanisms, including effects on the hypothalamus, the pituitary and the adrenal glands.[21–26] The symptoms of hypogonadism, including sexual dysfunction, fatigue, depression, and osteoporosis, are non-specific. Their onset may be gradual, and neither patient nor clinician may consider medication as a cause. Some patients are reluctant to report sexual dysfunction, so it may often go unrecognized and untreated.[27,28]

Hypogonadism and erectile dysfunction appear to be only loosely associated.[29] However, the use of medications for erectile dysfunction or testosterone replacement generally implies clinically important sexual dysfunction. We therefore studied the use of medications for erectile dysfunction or testosterone replacement as proxies for sexual dysfunction among men receiving opioid or non-opioid therapy for pain. We focused on men with back pain, because back pain is a leading reason for opioid use;[30] is common at an age when adults are sexually active; reduces confounding by disease-related causes of both pain and sexual dysfunction (e.g. diabetic neuropathy); and provides a relatively homogeneous sample for comparing subgroups of opioid users and non-users.

Our aims were:

1. To examine the prevalence of use of medications for erectile dysfunction or testosterone replacement according to duration and dose of opioid therapy
2. To determine whether use of medications for erectile dysfunction or testosterone replacement was associated with a diagnosis of depression, other comorbid conditions, or with smoking among patients with pain
3. To determine whether use of medications for erectile dysfunction or testosterone replacement was associated with opioid dose and duration after adjusting for age, depression, smoking, and medical comorbidities.

MATERIALS AND METHODS

General

The setting and methods of data collection and database assembly have been described elsewhere.[16] This analysis examined only the male subset of the earlier study population.

We provide here only a summary of those methods, along with a description of the unique features of this analysis.

Setting

XXXX (XXXX) is an integrated health care system based in XX, XXn, serving more than 470,000 members. XXXX provides a full scope of primary and specialty care for members.

Each member receives a medical record number on enrollment, which remains with that patient even through gaps in membership. Electronic health record data systems are accessible for research purposes, and this study was approved by the Institutional Review Boards at the XX Center for Health Research and at XX University.

XXXX offers reduced prices on prescription medications, and prescriptions are prepaid for a substantial proportion of members. The electronic pharmacy system records all dispensed medications. A membership survey indicated that approximately 90 percent of prescriptions are filled at a XXXX pharmacy, even for members without a prepaid drug benefit. For this study, we required that patients have at least one year of continuous membership and medication coverage prior to the index visit. Because of these features and requirements, patients had financial and logistical incentives to use program pharmacies to fill prescriptions.

Patients

We studied ambulatory adult men aged 18 and over. To select patients with back pain, we chose as an index visit the first visit in 2004 with any one of 32 ICD-9 diagnoses known to be associated with low back pain.[16,31] We excluded those with evidence of underlying systemic disease or trauma. Including patients with even a single visit for back pain resulted in a mix of patients with acute, subacute, and chronic pain.

Defining Episodes and Doses of Opioid Use

For this purpose, we analyzed electronic pharmacy and medical record data for 6 months before and after an index visit. Using earlier definitions, patients' opioid use was characterized as "none", "acute" (≤ 90 days),"episodic", or "long-term" (≥120 days or > 90 days with 10 or more fills). Episodic use was for greater than 90 days, but less than 120 days, and with less than 10 fills of opioid medication.[32] We classified opioids as long or short acting, and calculated approximate morphine equivalents for each prescription, following Von Korff and colleagues.[32]

Medications for Erectile Dysfunction

We considered prescriptions for sildenafil, tadalafil, and vardenafil that were filled within 6 months before or after the index visit. We also considered prescriptions for testosterone replacement, including testosterone enanthate, testosterone cypionate, testosterone proprionate, topical and buccal testosterone preparations, methyltestosterone, oxandrolone, and fluoxymestrone.

Measures of patient comorbidity and health care use

We recorded several patient demographics, comorbid conditions and health habits, and co-prescription of sedative hypnotics. We grouped body mass index (BMI) as <25 (ideal), 25–29.9 (overweight), or >30 (obese). The sedative hypnotics included benzodiazepines (80% of prescriptions), barbiturates, the so-called "z-medications" (zolpidem, eszopiclone, zaleplon), carisoprodol, and less frequently prescribed medications (diphenhydramine, chloral hydrate, meprobamate, and others).[33,34] We searched medical records for one year

prior to the index visit for any coded ICD-9-CM diagnoses for depressive disorder (296.2, 296.3, 300.4, 309.0, 309.1, 311). These diagnoses were not based on standardized measures, but on clinicians' judgments.

Comorbidity was measured using the RxRisk score, a pharmacy-based risk assessment model designed to predict future health care costs based on patient age, sex, Medicare or Medicaid insurance coverage, and use of medications closely linked to specific chronic conditions (eg, biguanides, insulins, sulfonylureas for diabetes).[35,36] The score is calculated from a regression model that weights each diagnosis according to its ability to predict future costs. For adults, the RxRisk calculation excludes analgesics, because they are prescribed with too much discretion to be appropriate for a payment adjustment model.[35] We also tabulated the number of hospitalizations in the past year as a crude marker of illness burden.

Analysis

We used The Cochrane-Armitage test for trend to compare proportions across ordered categories of opioid use. For continuous variables, we used the independent samples t-test and Kruskall-Wallis nonparametic rank-sum test where appropriate. Chi-square tests for categorical variables were used to assess differences in patient characteristics between men using and not using medications for erectile dysfunction or testosterone replacement. The association between opioid use and prescriptions for erectile dysfunction or testosterone replacement was examined using multiple logistic regression, adjusting for patient age, comorbidity score, number of hospitalizations, sedative-hypnotic use, duration of opioid use, morphine dose at last dispensing, type of opioid (long- or short-acting), depression, and smoking status. Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC), and all tests were 2-sided with alpha set at 0.05.

RESULTS

Subjects

There were 11,327 men enrolled in XXXX with a diagnosis of back pain on at least one visit in 2004. Their mean age was 48.6 years. Data on race were missing for almost 41%, but 89.3% of those with recorded race were white. The remainder included 2.9% Black; 2.6% Asian or Pacific Islander; 1.2% American Indian or Alaska Native; and 3.9% other. Regarding ethnicity, 3.4% listed their ethnicity as Hispanic.

Characteristics of men who did and did not use medications for erectile dysfunction or testosterone replacement

Men who were prescribed medications for erectile dysfunction or testosterone replacement ($n = 909$) were significantly older than those who were not (mean age 55.7 years vs. 48.0 years, $p<0.01$). Similarly, men who used these medications had significantly greater medical comorbidity, prevalence of depressive disorder diagnoses, and use of sedative-hypnotic medications (Table 1). There also were significantly fewer never-smokers among the men using medications for erectile dysfunction or testosterone replacement.

Association of medications for erectile dysfunction, depression, and smoking with opioid duration and dose

The probability of receiving medications for erectile dysfunction or testosterone replacement both increased consistently with increasing duration of opioid therapy (Table 2). Prescriptions for erectile dysfunction were several times more common than prescriptions for testosterone replacement. When combined, these medications were prescribed for 13.1% of men receiving long-term opioids.

Prescriptions for sedative-hypnotic medications also increased consistently with increasing duration of opioid therapy, as did diagnoses of depression and the prevalence of smoking (Table 2).

Prescriptions for erectile dysfunction or testosterone replacement increased with increasing dose as well as duration of opioids. This was true within each category of opioid duration (Table 3). For patients receiving long-term opioids at doses greater than 120 morphine equivalents/day, over 19% also received prescriptions for erectile dysfunction or testosterone replacement, in contrast to 12.5% of patients receiving long term opioids at lower doses, and 6.7% of patients with back pain but no opioid therapy.

When we grouped body mass index (BMI) as <25 (ideal), 25–29.9 (overweight), or >30 (obese), it was significantly associated with use of medications for erectile dysfunction or testosterone replacement (6.8%, 7.9%, and 9.9% of patients using these medications, respectively, p<.0001). However, When added to our multivariate model, BMI was not independently associated with use of these medications (OR for obese vs. ideal weight, 1.12, 95% CI 0.9, 1.4, p=.26).

In the logistic regression model, age was the characteristic most strongly associated with use of medications for erectile dysfunction or testosterone replacement (Table 4). Use of these medications also increased consistently with increasing levels of medical comorbidity. However, even after adjustment for these factors, long-term opioid use was associated with greater use of medications for erectile dysfunction or testosterone replacement, compared to patients with no opioid use (OR 1.45, 95% CI 1.12, 1.87, p<0.01).

Similarly, patients who were prescribed daily doses of 120 mg morphine equivalent or more had an odds ratio of 1.58 (95% CI 1.03, 2.43), even with duration of opioid therapy in the model. However, lower doses of opioids were not associated with a higher odds ratio in this multivariate model. Thus, the combination of long term and high dose opioid use seems most strongly associated with markers of sexual dysfunction. With dose and duration in the model, the use of long-acting vs. short-acting opioid preparations was not associated with these markers of sexual dysfunction.

Depressive disorders (OR 1.30, 95% CI 1.06, 1.60, p=0.01) and the use of sedative-hypnotics (O.R. 1.30, 95% CI 1.08–1.56, p=0.006) were also independently associated with use of medications for erectile dysfunction or testosterone replacement (Table 4). Although smoking status was strongly associated with duration of opioid use, after adjustment for other variables in the model, smoking status was no longer significantly associated with use of medications for erectile dysfunction or testosterone replacement.

DISCUSSION

We found that medication prescriptions for erectile dysfunction or testosterone replacement were associated with both the dose and duration of opioid therapy. For patients receiving high-dose long-term opioids, over 19% had such evidence of sexual dysfunction. A significant association with opioid duration persisted even after adjusting for age, medical comorbidity, markers of psychological distress, and other factors. Both long-term use of opioids and high-dose opioid therapy were associated with roughly 50% greater odds of using medications for ED or testosterone replacement after adjusting for such confounders. However, age, depression, overall comorbidity, and use of sedative-hypnotics were also independently associated with the use of medications for erectile dysfunction or testosterone replacement.

In multivariate models, obesity and smoking were not independently associated with use of medications for erectile dysfunction or testosterone replacement. This may be because obesity and smoking are also associated with depression, comorbidity, and use of opioids, all of which were retained in the model.

Other studies have reported an increasing rate of hypogonadism with increasing doses of opioids, but without adjustment for opioid duration or other potential confounders.[9] We cannot equate the use of medications for erectile dysfunction with the occurrence of hypogonadism for several reasons. First, in studies with hormone measurement, erectile dysfunction and hypogonadism appear to be only loosely related.[29] Second, we found that depression and use of sedative-hypnotics were also associated with these markers of sexual dysfunction. Third, other factors, such as age and comorbidity, were important correlates of both opioid use and apparent sexual dysfunction.

Use of medications for erectile dysfunction or testosterone replacement as a marker of sexual dysfunction may underestimate its actual prevalence among men with chronic pain or prescription opioid use. Some studies of long-term opioid use with hormone measurement have reported higher rates of hypogonadism than our data might suggest, though the study samples may have been self-selected.[9,19] Furthermore, both sexual dysfunction and hypogonadism may be under-diagnosed, due to reluctance to report symptoms,[27] gradual onset,[28] and failure of physician or patient to associate symptoms with medication use.[39] It seems unlikely that evidence of sexual dysfunction in our patients was due to pain alone, because even the patients without opioid use had back pain.

This study has the advantages of providing data from a large population, from many providers, and with nearly complete capture of healthcare utilization. It provides information on sexual dysfunction in an unselected sample of patients with back pain. It also provides new information on the association of sexual dysfunction with depressive disorders, smoking, use of sedative-hypnotics, and comorbidity -- as well as opioid use -- among patients with chronic pain.

However, it also has some limitations. Although every patient had back pain, we do not know the original indication for prescribing opioids. Clinical experience suggests that this may often be unclear for long-term opioid users, even when the full medical record is examined. Furthermore, many patients have multiple pain conditions, and it may be misleading to single out one diagnosis.[40] We cannot know the degree to which the associations we found are causal or the direction of any causation. Because medication use was measured for 6 months before and after the index back pain visit, sexual dysfunction (and related medication use) may have preceded the use of opioid therapy. Thus, the cross-sectional design of our study is another important limitation. However, the graded association of the duration and dose of opioid use with use of medications for erectile dysfunction strengthens an argument for causal associations. Our dataset did not include all patient diagnoses, and we could not identify individuals who also had diabetes, a potentially confounding cause of erectile dysfunction. However, our comorbidity score included adjustment for diabetes and other comorbid conditions (as reflected by medication use), so the associations we observed are at least partly adjusted for this condition.

For researchers, our data suggest that age, comorbidity, depression, and sedative-hypnotic use must all be considered when examining the association of opioid use with sexual dysfunction. For clinicians, our data provide a reminder that information on sexual dysfunction should be part of clinical decision-making with regard to long-term pain management, and provide some evidence regarding its prevalence. Both patients and clinicians should recognize possible opioid effects on sexual functioning in considering

treatment options. Further, some evidence suggests that identifying and treating sexual dysfunction and possible hypogonadism among chronic opioid users may reduce pain and depression, minimizing opioid requirements.[41] Obtaining better information on sexual dysfunction among patients with chronic pain remains a high priority for future research.[23]

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Key Points

1. Men with chronic pain may experience erectile dysfunction related to depression, smoking, age, or opioid-related hypogonadism. The prevalence of this problem in back pain populations and the relative importance of several risk factors are unknown.
2. Among 11,327 men in an integrated health plan, 909 received medications for erectile dysfunction or testosterone replacement. Use of these medications was independently associated with age, comorbidity, depression, use of sedative-hypnotics, and use of opioid analgesics
3. Use of medications for erectile dysfunction or testosterone replacement was related to both opioid dose and duration. Among patients using long-term opioids at doses over 120 mg. morphine-equivalents/day, 19% used medications for erectile dysfunction or testosterone replacement.
4. For researchers, our data suggest that age, comorbidity, depression, and sedative-hypnotic use must all be considered when examining the association of opioid use with sexual dysfunction. For clinicians, our data provide a reminder that information on sexual dysfunction should be part of clinical decision-making with regard to long-term pain management.

Table 1

Characteristics of men with back pain who were or were not prescribed medications for erectile dysfunction or for testosterone replacement

Patient Characteristic		Prescribed medications for Erectile Dysfunction and/or Testosterone Rx	
		Yes (n=909)	No (n=10,418)
Age, Mean± SD [a]		55.7 ± 11.3	48.0 ± 15.9
RxRisk Comorbidity Score, Number (%) [a]	First quartile[b]	179 (19.7)	4,366 (41.9)
	Second quartile	180 (19.8)	2,054 (19.7)
	Third quartile	281 (30.9)	2,062 (19.8)
	Fourth quartile	269 (29.6)	1,936 (18.6)
Sedative/Hypnotic Use, Number (%) [a]		222 (24.4)	1,627 (15.6)
Diagnosis of Depression, Number (%)[a]		157 (17.3)	1181 (11.3)
Smoking Status, Number (%) [a]	Never-smoker	225 (25.7)	3,282 (34.0)
	Smoker	206 (23.6)	2,298 (23.8)
	Quitter	443 (50.7)	4,066 (42.2)

[a] $p<0.01$ for comparison of patients using or not using medications for erectile dysfunction or testosterone replacement.

[b] Comorbidity Score (RxRisk) quartiles:

First quartile: 70.69–658.1

Second quartile: 658.11–1,670.79

Third quartile: 1,670.80–3,268.09

Fourth quartile: 3,268.10–48,554.29

Table 2

Prescription drug use among men with back pain, by duration of opioid use

Type of health care use	No opioids	Acute opioids only	Episodic opioid use	Chronic opioid use	p-value (subgroup differences)
n of subjects	4,655	4,696	164	1812	
Median opioid dose at last dispensing, morphine equivalent	NA *	30.0 mg	20.0 mg	30.0 mg	<0.0001
Long-acting opioids, n (%)	NA *	75 (1.6)	25 (15.6)	744 (41.8)	<0.0001
Sedative-hypnotic prescription in 6 mos before/after index visit, n (%)	330 (7.1)	783 (16.7)	51 (31.1)	685 (37.8)	<0.0001
Rx for sildenafil, tadalafil, or vardenafil, 6 mos before or after index visit, n (%)	294 (6.3)	324 (6.9)	12 (7.3)	204 (11.3)	<0.0001
Testosterone replacement medications 6 mos. before or after index visit, n (%)	25 (0.5)	30 (0.6)	2 (1.2)	44 (2.4)	<0.0001
testosterone replacement OR drug for erectile dysfunction, n (%)	312 (6.7)	346 (7.4)	13 (7.9)	238 (13.1)	<0.0001
Current smoker, n (%)	757 (18.0)	1,120 (25.3)	38 (25.3))	589 (33.6)	<0.0001
Depression, n (%)	362 (7.8)	526 (11.2)	27 (16.5)	423 (23.3)	<0.0001

* Not applicable. This category not included in tests of statistical significance.

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Table 3

Prevalence of drug prescriptions for erectile dysfunction or testosterone replacement according to dose and duration of opioid use. Tabled figures represent n with prescription for erectile dysfunction or testosterone replacement/total in cell (%).

Opioid dose*	Opioid Duration			
	None	Acute	Episodic	Chronic
N	4,655	4582†	161†	1805†
None	312/4655 (6.7)	-	-	-
1 to <20 mg.	-	88/1215 (7.2)	4/80 (5.0)	70/559 (12.5)
20 to <120 mg.	-	242/3315 (7.3)	7/75 (9.3)	133/1065 (12.5)
≥120 mg.	-	4/52 (7.7)	1/6 (16.7)	35/181 (19.3)

*Opioid dose in morphine equivalents/day for last opioid prescription in study interval

†These numbers are slightly less than Table 2 due to missing data on opioid dose. This occurred because 124 patients (1%) were receiving opioid medications during the study year from prescriptions written before the study year, and doses for those prescriptions were not captured in the dataset. Over 90% of the missing dose information was for acute duration opioid use.

Table 4

Logistic regression model results for use of medications for Erectile Dysfunction or Testosterone Replacement, men only

Variable	Odds Ratio	95% Wald CI	*Overall p for variable*
Opioid episode duration			0.007
No Use (reference)	1.00	1.00	
Acute Use	1.02	0.81–1.28	
Episodic Use	0.83	0.43–1.58	
Chronic Use	1.45	1.12–1.87	
Age			<0.0001
18–29	1.00	1.00	
30–39	2.76	1.44–5.32	
40–49	6.45	3.48–11.95	
50–59	11.75	6.36–21.70	
60–69	14.37	7.65–27.02	
70+	6.83	3.54–13.19	
Co-morbidity Score *			0.006
First quartile	1.00	1.00	
Second quartile	1.25	0.99–1.59	
Third quartile	1.51	1.20–1.91	
Fourth quartile	1.48	1.13–1.93	
Hospitalizations			0.02
0	1.00	1.00	
1	0.69	0.52–0.91	
2	0.55	0.31–0.97	
3+	0.99	0.49–1.98	
Sedative/Hypnotics(GPI+AHFS)			0.006
No	1.00	1.00	
Yes	1.30	1.08–1.56	
Morphine Daily Dose †			0.09
0 to <20	1.00	1.00	
20 to <120	1.01	0.83–1.25	
≥120	1.58	1.03–2.43	
Type of Opioid			0.5
Short acting only	1.00	1.00	
Long acting	0.90	0.67–1.21	
Depressive disorder			0.01
No	1.00	1.00	
Yes	1.30	1.06–1.60	
Smoker			
No	1.00	1.00	0.4
Yes	1.06	0.91–1.23	

[*] Comorbidity Score(RxRisk) quartiles:

First quartile: 70.69–658.1

Second quartile: 658.11–1,670.79

Third quartile: 1,670.80–3,268.09

Fourth quartile: 3,268.10–48,554.29

[†] Daily dose in morphine equivalents at last dispensing prior to index visit