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Erectile Dysfunction in Opioid Users: Lack of Association with Serum Testosterone

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Abstract

This study describes the prevalence of erectile dysfunction (ED) among 57 men using illicit opioids who presented to a primary care program for buprenorphine therapy. Participants' mean age was 40 years and 34% reported ED. Low total testosterone was detected in 17% of those reporting ED , but total testosterone was not significantly associated with ED. Examining multiple comorbidities and laboratory parameters, only older age was significantly associated with erectile dysfunction (r=.27, p<.05). ED is highly prevalent among males abusing opioids, but low total testosterone is rarely the cause.

Keywords

Erectile Dysfunction; Opioid; Serum Testosterone

Introduction

Erectile dysfunction (ED), defined as the inability to achieve and/or maintain an erection satisfactory for the completion of sexual activity[1], is a highly prevalent health condition affecting males in the United States[2]. Numerous studies have examined the prevalence of erectile dysfunction in the general population[2-5]. In the general population, the literature suggests prevalence rates ranging from 18.4-52% across all age groups[2-6].

Men who chronically use opioids report an unexpectedly high prevalence of erectile dysfunction and at younger ages compared to the general population. Across several published reports, in males with a mean age of 28-49 years, prevalence rates of ED ranged from 21-52% [7-12]. The highest rates of ED were reported in men maintained on methadone (Hallinan et al., Quaglio et al.), followed by those using heroin (Bang-Ping) and lastly by those maintained on buprenorphine (Hallinan et al., Quaglio et al.).

In a cross-sectional study of 201 men with a mean age of 31 years, Quaglio et al. found that 42% of men receiving methadone maintenance or buprenorphine reported symptoms of ED[12]. Men receiving methadone maintenance had a higher prevalence than those receiving buprenorphine (50% vs. 36%, respectively). Higher depression scores were associated with ED; however dosage, duration of treatment, age, and education level were not. Similarly, Hallinan et al. found a higher prevalence of ED in men taking methadone than those on

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buprenorphine therapy (52% vs. 21%, respectively)[10]. In this cross-sectional study, older age, lower total testosterone levels, and depression symptoms were associated with ED. Hanbury et al. found a 33% prevalence of sexual dysfunction among 50 men participating in a cross-sectional study who had received 24 months of methadone treatment with a mean dose of 62mg daily[11]. Interestingly, 71% of these men had experienced similar difficulties while using illicit opioids (heroin).

The NIH Consensus panel on impotence recommends routine screening of morning serum testosterone levels in the evaluation of men presenting with symptoms of erectile dysfunction[1]. Yet most studies fail to demonstrate an association between erectile dysfunction and serum testosterone, especially in younger men[3, 13-17]. The prevalence of hypogonadism, defined as persistently low levels of serum testosterone[18], is generally low (less than 5%) in men presenting for treatment of erectile dysfunction[19]. However, few studies have examined the relationship of testosterone to erectile dysfunction in males abusing illicit opioids.

Two studies reported that 44-64% of men on methadone maintenance had low serum total testosterone levels[20-21]; however, Daniell found that low total testosterone was not significantly related to erectile dysfunction. Hallinan et al. found low total testosterone in two-thirds of men on methadone and one-third of men on buprenorphine, and that low total testosterone was associated with erectile dysfunction[10]. In a sample of 54 methadone-maintained males with ED, Bliesener et al. found that while average total testosterone was low, total testosterone levels in men on buprenorphine did not differ significantly from healthy controls[22].

Only one study has reported rates of ED among men using illicit opiates who were not in treatment. Bang-Ping, interviewing 276 heroin users with a mean age of 36 years, noted an ED prevalence of 44%. ED was not associated with smoking status, but was associated with older age[7]. This cohort did not include prescription opioid abusers and did not measure levels of testosterone.

This cross-sectional study was designed to assess the prevalence of erectile dysfunction and identify factors associated with ED among opioid-dependent men presenting to a primary care setting for buprenorphine therapy. Because the effect of androgen levels on erectile dysfunction remains unclear and the value of routine screening of testosterone levels in this setting remains controversial, we also examined whether ED in opioid-dependent men was related to serum testosterone levels.

Methods

Between December 2006 and June 2008, 63 adult male patients initiated buprenorphine treatment in a primary care office as part of a treatment outcome study. To be eligible for the buprenorphine program, patients had to report: (1) opioid dependence or receiving methadone maintenance at doses less than 35mg/day; (2) alcohol use less than NIAAA hazardous levels[23]; (3) cocaine use no more than twice weekly; (4) no benzodiazepine dependence; and (5) willingness to remain in treatment for at least 6 months. In the current analysis, 6 men were excluded due to missing data, leaving a sample size of 57. All participants provided written informed consent to participate and the study was approved by the Rhode Island Hospital Institutional Review Board.

Demographic data including age, race, height, and weight were collected. The medical history, including co-morbidities such as diagnosed diabetes, hypertension, coronary artery disease, and smoking history was obtained. A substance abuse history assessed the participants' current opioid of choice and total years of use, as well as use of other drugs in the past 30 days. The Beck Depression Inventory (BDI)[24] was used to measure depressive symptoms. No

participants were using medications for either erectile dysfunction or depression at the time of enrollment.

At the initial visit, prior to receiving buprenorphine, participants were asked a single question taken from the International Index of Erectile Function (IIEF)[25] to evaluate for the presence of erectile dysfunction. Participants were asked: "Over the past 4 weeks, how often were you able to get an erection during sexual activity?" Possible responses were: "0" not sexually active, "1" almost never/never, "2" less than half the time, "3" sometimes/half the time, "4" most times, "5" almost always/always. The validity of a single question assessment of erectile dysfunction has been previously demonstrated[26].

Following the initial interview, participants underwent phlebotomy. Non-fasting laboratories including a hepatitis panel, liver enzymes, and a complete blood count were obtained. Also, serum levels of total testosterone (TT, normal range: 270-1070 ng/dl; by chemiluminescence method, Siemens Centaur assay; sensitivity range: 10-1500 ng/dl) were measured. Blood samples were obtained in the morning to avoid diurnal variations in the assay.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences Version 17.0[27]. Descriptive statistics including means, proportions and standard deviations were calculated. To examine the correlation between the outcome variable (erectile dysfunction) and the continuous and categorical predictor variables, Spearman correlation coefficient and chi square statistics were used, respectively.

Because other studies have dichotomized ED[5, 8, 11, 16] and we felt it was clinically relevant to do so, we dichotomized the outcome variable into the presence or absence of ED, with the former category including responses 1 to 4 on the ED question. Men who were not sexually active in the past 4 weeks (indicated by responding 0 on the ED question) were excluded from the analysis (n=4). To examine for potential differences between the 2 groups (men who reported the presence of ED and those who did not), the t-test statistic was calculated for normally distributed variables and the Mann-Whitney U was calculated for the non-normal distributions. Logistic regression analysis was used to perform adjusted analyses for the binary outcome of erectile dysfunction. Two-tailed probability values are reported.

Results

Demographic and clinical characteristics of the sample are presented in Table 1. The 57 participants averaged 40.8 (+/- 9.9) years of age; 82.5% were Caucasian, and 80.7% were current smokers. Heroin was the primary opioid of choice for 52.6% of the participants; 28.1% and 19.3% used prescription opioids and methadone, respectively. Mean duration of opioid use was 11.9 (+/-9.4) years. Alcohol was consumed at least once in the past 30 days by 42.1% of the participants. In addition, 35.1%, 33.3%, and 26.3% of the sample had used cocaine, marijuana, or benzodiazepines, respectively, at least once in the past 30 days.

Hepatitis C antibody was positive in 49.1% of participants and 29.8% had abnormal liver enzymes. Anemia, defined as a hemoglobin level less than 13.5 g/dl, was found in 10.7% of participants. No participants were Hepatitis B surface antigen positive. One participant had Type 2 diabetes and one participant had a history of myocardial infarction.

Overall, 34% of participants reported erectile dysfunction. In the group of men aged 40 or less (n=28), erectile dysfunction was reported by 25%. Among men greater than age 40 (n=25), 44% reported ED. There were no significant associations between erectile dysfunction, total

testosterone, BMI, baseline BDI, smoking, opioid of choice, or duration of opioid use. A positive correlation was found (r = .27, p < .05) between older age and erectile dysfunction.

In the between-groups analysis, age, mean BMI, mean baseline BDI, and duration of opioid use did not differ significantly between men with and without ED (Table 1). The ED and non-ED groups had similar mean total testosterone levels (412.8 vs. 454.0, p=0.54) Seven men (13.2%) in the cohort had total testosterone levels below the lower limit of normal; three reported ED and 4 did not (p=0.32). Race, opioid of choice and smoking status was not significantly different between these two groups. In addition, there was no significant difference between the groups with regard to presence of anemia (p=0.17), hepatitis C status (p=0.32), abnormal liver enzymes (p=0.72), or the use of alcohol (p=0.14), benozodiazepines (p=0.69), marijuana (p=0.38) or cocaine (p=0.38) in the past 30 days. The results of the logistic regression analysis did not differ from the unadjusted analyses.

Discussion

In this study of active illicit drug users, we found an ED prevalence of 34%, similar to other studies of men receiving opioid substitution treatment[10-12] and the one study of heroin users[7]. Examining a broader array of variables than considered by other authors, we found that only one factor, age, was significantly associated with erectile dysfunction.

The overall prevalence of ED in our study was quite high considering that the mean age of this cohort was only 40 years. Indeed, the prevalence of ED in men younger than 40 years was 25% here, far higher than that reported in the general population. In the NIH consensus statement, the reported prevalence in men younger than 40 was 5%[1]. Increased ED prevalence has been consistently associated with older age with prevalence rates as high as 52% in men over the age of 50[2-4]. In our cohort, ED was significantly correlated with older age, similar to findings in men taking methadone or buprenorphine[8, 10] or using heroin[7].

Of interest, although hormonal assays are recommended as part of the initial evaluation of males with symptoms of ED[1], we did not find a relationship between total testosterone levels and erectile dysfunction. Mean total testosterone levels in the groups with and without ED were not significantly different (p=0.32) and only 17% (3/18) of persons with ED had low serum testosterone levels. This is consistent with previous studies that also did not show an association between testosterone and erectile dysfunction[8, 13, 15-17, 20].

Of note, serum total testosterone measures do not necessarily reflect biologically available testosterone, a more accurate marker of hypogonadism. Previous studies have shown that smoking and chronic Hepatitis C infection (both highly prevalent in this population and in our cohort) may increase levels of sex hormone binding globulin (SHBG), resulting in elevated total testosterone levels yet lower bio-available testosterone[28-30]. The resultant alteration in androgen levels may produce a state of hypogonadism, with symptoms of ED, in the presence of normal total testosterone levels. In addition, some have suggested using age-adjusted total testosterone levels to determine normal ranges for males[31-32].

We do not have an explanation for the high rates of ED among these young, opioid dependent men. Heroin use can cause acute suppression of LH release from the pituitary leading to a secondary drop in testosterone levels[33]. High rates of smoking may also play a role as some studies report twice the prevalence rate of ED in smokers compared to nonsmokers[5, 34]. Our cohort also reported extremely high levels of depressive symptoms; however, in multivariate analyses, baseline BDI was not significantly associated with erectile dysfunction . Still, in the absence of biological etiologies, psychiatric disorders that were not assessed here may play an important role in ED.

This study has potential limitations. The sample was small, limiting the study's power to detect associations. Although only four men were not sexually active in the past 4 weeks, their exclusion from the analysis may have biased the prevalence of ED downward as men without partners may have a higher rate of ED[3, 12]. Testosterone levels were measured only once—most consensus guidelines recommend at least two morning samples. One study showed normalization of TT on second analysis in 40% of their sample[19]. Also, the definition of ED is more conservative in some studies which included only those men that indicate poor or very poor erectile function. We chose a less conservative definition including men with all levels of ED. Furthermore, we did not ask their frequency of sexual activity nor did we know the duration of their ED. Because our ED question was administered in person by a female interviewer, some participants might not have reported accurately. The responses given to female interviewers may be different from those given to male interviewers, especially when sexual history information is being elicited[35]. Due to the sensitive nature of the information, the use of a self-report instrument might have yielded an even higher rate of ED. Finally, these findings might not generalize to opioid-using populations who are also dependent on other substances such as benzodiazepines, amphetamines, cocaine or alcohol since these were study exclusions.

We conclude that there is a high prevalence of erectile dysfunction among opioid-dependent males prior to initiating substance abuse treatment with buprenorphine. No published studies to date have examined ED symptoms over time in males using opioids. Longitudinal studies are needed to determine if ED symptoms in men improve over time following discontinuation of opioid use or if stabilization in maintenance treatment using buprenorphine therapy improves symptoms of erectile dysfunction. While our data and others' suggest that erectile dysfunction does not seem to correlate with total testosterone levels, repeatedly low testosterone levels is a clinically important and treatable cause of ED. Although current guidelines recommend obtaining testosterone levels in all men reporting ED, these findings suggest that further study, especially of costs and benefits, is warranted to support this recommendation in younger opioid-using men.

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Table 1

Demographics of Sample & Unadjusted Differences between Groups

	Total Sample N=57 (mean, SD)	No ED** n=35 (mean, SD)	ED** n=18 (mean, SD)	P value
Age	40.8, 9.9	39.1, 9.2	41.0, 9.5	0.49
BMI	26.7, 3.8	26.8, 3.7	26.4, 4.1	0.64
TT (ng/dl)	431.1, 204.9	454.0, 177.0	412.8, 273.3	0.54
B. BDI	25.2, 9.9	26.4, 9.0	22.7, 12.1	0.22
Duration of Opioid Use* (years)	11.9, 9.4	11.9, 9.3	10.6, 8.8	0.67
Race (n, %)				0.12
White	47 (82.5%)	28 (80%)	17 (94%)	
Black	3 (5.3%)	0 (0%)	1 (6%)	
Hispanic	5 (8.8%)	5 (14%)	0 (0%)	
Other	2 (3.5%)	2 (6%)	0 (0%)	
Opioid of Choice (n, %)				0.86
Heroin	30 (52.6%)	18 (51%)	9 (50%)	
Pills	16 (28.1%)	9 (26%)	6 (33%)	
Methadone	11 (19.3%)	8 (23%)	3 (17%)	
Smoking Status (n, %)				0.65
Smoker	46 (80.7%)	29 (83%)	14 (78%)	
Nonsmoker	11 (19.3%)	6 (17%)	4 (22%)	

*Mann-Whitney U test statistic

**"not sexually active" = 4 (excluded from analysis)