Erectile Dysfunction in Men Receiving Methadone and Buprenorphine Maintenance Treatment

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ABSTRACT

Introduction. Use of opiates/opioids is associated with hypoactive sexual desire, erectile and orgasmic dysfunction.

Aim. To determine prevalence and investigate etiology of sexual dysfunction in men on methadone or buprenorphine maintenance treatment (MMT, BMT).

Main Outcome Measures. International Index of Erectile Function (IIEF), hormone assays, Beck Depression Inventory.

Methods. A total of 103 men (mean age 37.6 ± 7.9) on MMT (N = 84) or BMT (N = 19) were evaluated using the IIEF, hormone assays, Beck Depression Inventory, body mass index (BMI), demographic, and other substance use measures.

Results. Mean total IIEF scores for partnered men were lower for MMT (50.4 ± 18.2; N = 53) than reference groups (61.4 ± 16.8; N = 415; P < 0.0001) or BMT (61.4 ± 7.0; N = 14; P = 0.048). Among partnered men on MMT, 53% had erectile dysfunction (ED) compared with 24% of reference groups; 26% had moderate to severe ED, 12.1% in under 40s and 40.0% among those 40+ years. On multiple regression, depression, older age, and lower total testosterone were associated with lower IIEF and EF domain; on multivariate analysis, there were no significant associations between IIEF or EF and free testosterone, opioid dose, cannabis or other substance use, viral hepatitis, or BMI. Total testosterone accounted for 16% of IIEF and 15% of EF variance. Men without sexual partners had lower Desire and Erection Confidence scores and less recent sexual activity, suggesting potentially higher prevalence of sexual dysfunction in this group.


Key Words. Erectile Dysfunction; Methadone; Buprenorphine; Opiate Addiction

Introduction and Aims

An extensive literature describes hypoactive sexual desire, erectile and orgasmic dysfunction associated with use of opiates/opioids [1]. Numerous early studies of methadone maintenance treatment (MMT) reported varying estimates of prevalence of sexual dysfunction, the majority of patients reporting either no changes or improvements in sexual function compared with heroin use [2–5]. One-third of 50 men reported sexual dysfunction shortly after initiating MMT, most of whom had experienced similar difficulties using heroin [6].

Three studies have reported higher rates of sexual dysfunction in men treated with methadone compared with healthy controls [7–9]. Bleisener et al. used a two-question self-rating scale [9].
Only two studies of sexual function in MMT have used a validated sexual function scale. Spring et al. used the Derogatis Sexual Functioning Inventory in 25 patients and Brown et al. used the Nowinski-Lopicollo Sexual History Form in 92 men [10,11]. Neither had a “healthy control” group.

With the exception of Hanbury et al., where subject selection was random within the clinic population, and Garbutt and Goldstein, who reported on 120 consecutive entrants to MMT, the above-cited studies lack sufficient subject selection details to demonstrate they were representative of men in MMT [4,6].

Several studies have reported no association between sexual dysfunction and methadone dose [8,11–13] although higher methadone dose correlated negatively with ejaculation frequency [14] and positively with orgasmic dysfunction in males on MMT [11].

In summary, it is difficult on the basis of the existing literature to draw conclusions about the prevalence of sexual dysfunction in men on MMT compared with the general population. The question of a methadone dose relationship to sexual dysfunction remains unresolved. Only one study has performed analysis of other factors (depression, other substance use, age, duration of treatment) which might play a role in symptoms of sexual dysfunction in MMT [11]. No previous study has examined other possible confounders such as chronic viral hepatitis and obesity. Only one study has examined sexual dysfunction in buprenorphine-treated men, reporting no difference from healthy controls [9].

Sexual dysfunction may be a factor motivating opioid-dependent people to cease heroin use or to leave MMT [4,15]. Of interest is the recent report that users of illicit drugs report a high prevalence of sexual disorders prior to first drug use (71%) and a factor in their decision to start taking drugs [16]. Following a number of cases of erectile dysfunction (ED) in men receiving MMT at the study practice, patients were regularly asked about sexual problems, which emerged as a reason for some patients prematurely leaving treatment or preferring subtherapeutic doses.

Therefore, we undertook a study to investigate sexual dysfunction in a representative cross-section of men on MMT or BMT for opiate dependency, with the aims of providing improved prevalence data for sexual dysfunction in this setting; and further to investigate the etiology of sexual problems by assessing the influence of other factors on sexual function in this population.

Our hypotheses were:

1. Sexual function measures differ between methadone, buprenorphine, and community reference groups, and . . .
2. Age, depression, obesity, chronic hepatitis, use of prescribed and nonprescribed substances, opioid medication, dose and duration of treatment, and/or hormonal status are associated with sexual function measures.

Methods

The study practice has been treating drug- and alcohol-dependent patients for 20 years and is located in a low socioeconomic area of inner Sydney [17]. At any one time, up to 170 patients are treated with MMT or BMT.

All men treated with MMT or BMT from this practice in December 2003 were invited to participate in the study. Exclusion criteria were: receiving antiviral treatment for viral hepatitis or HIV, or androgen replacement treatment; or newly in treatment (<8 weeks). Those who participated completed the International Index of Erectile Function (IIEF) and the Beck Depression Inventory (BDI) and were tested for total testosterone (TT), free testosterone (FT), estradiol (E2), luteinizing hormone (LH), and prolactin. Body mass index (BMI), opioid medication and dose, duration of current MMT or BMT, use of other medications, and serological and biochemical evidence of other significant illnesses, including hepatitis B and C (HBV, HCV) and HIV, were recorded at the time of pre- or posttest counseling, as were estimates of recent alcohol and other drug use. Alcohol use was recorded as average grams/day; tobacco smoking as average cigarettes/day; and benzodiazepine as average milligrams of diazepam-equivalent/day; cannabis, stimulant, or heroin use as days/month. Alcohol and other drug use information was obtained by clinical assessment, supported by urine toxicology, according to protocols which have been previously described [18].

The main outcome measures were the IIEF total score and EF domain.

Sexual Function: IIEF, Reference Groups, and Analysis

The IIEF is an extensively validated questionnaire covering five domains of male sexual function: EF, intercourse satisfaction, orgasm, desire, overall satisfaction [19].

As the IIEF contains a number of questions that are intercourse and partner dependent, data for
men with current sexual partners (defined as having a sexual partner(s) in the previous four weeks) were analyzed separately. The total score and the EF domain were analyzed only for this group. The sexual desire domain and erection confidence score, which are independent of recent sexual activity, were also examined for the entire patient group including men without current sexual partners. 

Results for the EF domain were classified according the method of Cappelleri et al. which distinguishes between men with and without ED, and provides classification of levels of ED severity [20].

Reference data for the IIEF were taken from the Study of Health Outcomes of Aircraft Maintenance Personnel (SHOAMP) which includes control groups from the Royal Australian Airforces bases at Amberley (\(N = 415\)) and Richmond (\(N = 530\)), as representative of community-dwelling male adults [21]. Similar to the findings of SHOAMP, preliminary analysis of the total IIEF scores in the present study were skewed to the left. For purposes of comparison the data were numerically transformed using the method described in SHOAMP, \(x = \log((\text{max} + 1) - y)\), where \(x\) and \(y\) are the values post- and pretransformation.

Methadone- and buprenorphine-treated men were compared separately with community reference groups for IIEF total scores. In order to determine factors associated with the main outcome measures, univariate regression and multiple (forward inclusion and backward stepwise) regression were carried out with total IIEF and the EF domain as the dependent factors and the following variables as independent factors:

- Opioid medication (buprenorphine vs. methadone)
- Methadone/buprenorphine dose
- Other substance use: tobacco, cannabis, heroin, stimulant, benzodiazepine, and alcohol consumption
- Age
- Duration of current opioid replacement treatment
- BMI
- BDI
- Chronic HCV infection defined by: positive HCV antibody with elevation of alanine aminotransferase (ALT); or positive HCV-RNA polymerase chain reaction assay
- ALT
- Hormonal indices: TT, FT, LH, E2, and prolactin

**Hormone Assays**

Hormonal assays used (detection limit; between-run coefficient of variation) were as follows: ADVIA Centaur® direct chemiluminescent immunoassays (Bayer Diagnostics, Tarrytown, NY, USA) for TT (0.35 nmol/L; 7.0%), LH (0.07 IU/L; 3.8%), E2 (36.7 pmol/L; 14.6%), and prolactin [0.3 ng/mL; 5.9%]; "Immulite®" chemiluminescent immunoassay (Diagnostic Products Corp., Los Angeles, CA, USA) for SHBG (0.02 nmol/L; 5.2%); and DSL-4900 radioimmunoassay (Diagnostic Systems Laboratories, Inc., Webster, TX, USA) for FT (0.3 pmol/L; 14.1%).

Preliminary analysis showed no difference between morning and afternoon collections for hormone indices in the study group. Therefore, data from afternoon collections were included for the regression analyses to increase statistical power.

**Statistical Analyses—General**

Exploratory data analysis was conducted using frequency distribution for categorical variables and graphs and summary statistics for continuous variables. Categorical variables were compared using chi-squared and continuous variables were examined using regression analysis and checked for homogeneity of variance. For samples that were not normally distributed, nonparametric \(t\)-test was used. Skewed distributions were transformed with the natural logarithm before the regression analysis. All statistical tests were two-tailed, and \(P \leq 0.05\) was considered as statistically significant. Statistical analyses were undertaken with STATA, version 8.2 (2003; Stata Corporation, College Station, TX, USA).

This study was approved by the Ethics Review Committee of the Central Sydney Area Health Service (CSAHS Protocol Nr X04-0051), and all subjects gave written consent for their participation.

**Results**

During December 2003, 128 men were prescribed MMT or BMT from the study practice, of whom 103 (80.5%) participated in the study. Nine men were excluded, being on antiviral treatment for HCV/HIV (3), on androgen replacement treatment (3), or newly in treatment (3), while 16 men did not participate, for reasons including difficult venepuncture (2) and unavailability for testing (6); six men declined to participate. Demographic and treatment details and use of other drugs are shown.
Sexual Dysfunction in Methadone Users

Table 1  Demographic and treatment characteristics, hormonal status, and other substance use

<table>
<thead>
<tr>
<th></th>
<th>Currently methadone</th>
<th>Currently buprenorphine</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed or student</td>
<td>37 (44.0%)</td>
<td>13 (68.4%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Pension, sickness benefit, unemployed</td>
<td>47 (55.9%)</td>
<td>6 (31.6%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Current partner</td>
<td>53 (63.1%)</td>
<td>14 (73.7%)</td>
<td>0.382</td>
</tr>
<tr>
<td>Age (mean years ± SD)</td>
<td>38.3 ± 8.2</td>
<td>36 ± 5.6</td>
<td>0.103</td>
</tr>
<tr>
<td>Duration of current continuous opioid treatment (mean months, SD)</td>
<td>67 ± 58</td>
<td>26 ± 27</td>
<td>0.009</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>24.6 ± 4.9 (23.8)</td>
<td>23.9 ± 4.1 (23.6)</td>
<td>0.560</td>
</tr>
<tr>
<td>HCV antibody</td>
<td>17.2 ± 10.2 (16.0)</td>
<td>17.0 ± 12.7 (18.0)</td>
<td>0.944</td>
</tr>
<tr>
<td>HCV antibody</td>
<td>66 (78.6%)</td>
<td>11 (57.9%)</td>
<td>0.061</td>
</tr>
<tr>
<td>Chronic HCV</td>
<td>48 (54.8%)</td>
<td>10 (52.6%)</td>
<td>0.793</td>
</tr>
<tr>
<td>ALT (mean, SD)</td>
<td>47 ± 36</td>
<td>65 ± 68</td>
<td>0.119</td>
</tr>
<tr>
<td>TT (mean ± SD, median)</td>
<td>11.6 ± 7.0 (10.7)</td>
<td>18.5 ± 8.7 (14.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>FT (mean ± SD, median)</td>
<td>28.6 ± 22.0 (20.4)</td>
<td>43.3 ± 37.2 (31.3)</td>
<td>0.037</td>
</tr>
<tr>
<td>LH (mean ± SD, median)</td>
<td>71.7 ± 51.3 (60.0)</td>
<td>76.0 ± 57.7 (62.0)</td>
<td>0.744</td>
</tr>
<tr>
<td>Prolactin ng/L (mean ± SD, median)</td>
<td>4.3 ± 5.5 (3.7)</td>
<td>4.3 ± 2.1 (4.3)</td>
<td>0.763</td>
</tr>
</tbody>
</table>

Other regular substance use

- Tobacco: 67 (79.8%) vs. 15 (78.9%) (P = 0.937)
- Alcohol: 28 (33.3%) vs. 10 (52.6%) (P = 0.115)
- Benzodiazepine: 28 (33.3%) vs. 3 (15.8%) (P = 0.132)
- Cannabis: 48 (57.1%) vs. 13 (68.4%) (P = 0.631)
- Stimulants: 20 (23.8%) vs. 7 (36.8%) (P = 0.243)
- Heroin: 20 (25%) vs. 5 (26.3%) (P = 0.818)

BMI = body mass index; HCV = hepatitis C; ALT = alanine aminotransferase; TT = total testosterone; FT = free testosterone; E2 = estradiol; LH = luteinizing hormone.

in Table 1. There was evidence of chronic HCV infection in 56/103 men (54.4%), of whom four had cirrhosis: in three of four the cirrhosis was compensated. One patient had HIV infection and two had chronic HBV (HBV surface antigen positive). Two men had diabetes mellitus (one insulin-dependent and one non-insulin-dependent). No men were taking antiretrovirals and 7/103 (6.8%) were taking antiretrovirals.

Buprenorphine- and methadone-treated men differed in respect of employment status (P = 0.055), duration of current continuous opioid treatment, TT, and FT.

IIEF

International Index of Erectile Function domains for men current sexual partners (N = 67), like those of SHOAMP and Rosen et al., were substantially correlated (data not shown) and therefore regression is reported here primarily on the total IIEF score and the EF domain [19,21].

The methadone group had significantly lower IIEF scores than SHOAMP groups and the buprenorphine group (Table 2). Mean ± SD IIEF domain scores (methadone; buprenorphine; maximum possible) for men with sexual partners are shown in Table 3.

Using the method of Capellieri et al. (IIEF EF domain scores ≤25 classified as ED) 52.8% of partnered men on methadone in the present study had some degree of ED compared with 21.4% of men receiving buprenorphine and 24% in both the Amberley and Richmond reference groups [20,21].

Prevalence of ED (EF score ≤ 25) among MMT men with partners was 15/33 (45.4%) for under 40s; 13/20 (65%) for those 40–60 years of age. Prevalence of moderate and severe ED (EF score 0–16) among MMT men with partners was 15/33 (45.4%) for under 40s; 8/20 (40.0%) for those 40+ years.

Among men with partners (mean age 39.4 ± 7.6, 6/67 (9.0%) had no sexual activity in the previous month, compared with 24/36 (66.7%) of those without partners (mean age 36.8 ± 7.9). Compared with men with partners, men without partners had significantly lower mean desire score (6.2; CI 5.7–6.6 vs. 4.4, CI 3.0–5.0; P < 0.0001) and erection confidence score (3.8; CI 3.6–4.1 vs. 3.1, CI 2.7–3.56; P = 0.003).

Regression Analyses

On univariate analysis, the following were significantly associated with the IIEF total score for men with sexual partners (r², P value): BDI (0.121, 0.004); TT (0.157, 0.001); and age (0.125, 0.003). Methadone vs. buprenorphine approached significance (0.075, 0.048). There were no significant associations of IIEF with FT, LH, E2, prolac-
tin, methadone dose, illicit opioid use, alcohol, tobacco, benzodiazepine or cannabis use, chronic viral hepatitis, ALT, or BMI.

Total testosterone, BDI, and age remained significantly associated with IIEF after forward inclusion and backward stepwise regression (Table 4). On removing TT from the multivariate model for IIEF score and substituting methadone vs. buprenorphine, BDI, and age, but not opioid medication, were significant.

Regressions were similarly performed for the ED domain. On univariate analysis, the following were significantly associated with the ED domain for men with sexual partners ($r^2$, $P$ value): BDI (0.109, 0.006); TT (0.146, 0.001); age (0.137, 0.002). Alcohol use approached significance (0.057, 0.051). TT, BDI, and age remained significantly associated with ED domain after forward inclusion and backward stepwise regression (Table 4). As for total IIEF, on removing TT from the multivariate model for ED score and substituting methadone vs. buprenorphine, BDI, and age, but not opioid medication, were significant.

Regressions were also performed for the desire domain scores and for erection confidence scores for the entire patient group. As with the total IIEF score, TT and BDI were significantly associated with desire domain scores and erection confidence after forward inclusion and backward stepwise regression (data not shown).

**Discussion**

**Prevalence of Sexual Dysfunction**

In this community-based drug dependency treatment clinic, men with current sexual partners on

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Age Mean ± SD</th>
<th>IIEF score total Mean ± SD (median)</th>
<th>IIEF total transformed* Mean ± SD (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone study group, partnered men</td>
<td>53</td>
<td>37.5 ± 8.4 (37.0)</td>
<td>50.4 ± 18.2 (57)</td>
<td>2.91 ± 0.82 (2.89)^2</td>
</tr>
<tr>
<td>Buprenorphine study group, partnered men</td>
<td>14</td>
<td>34.7 ± 5.2 (34.5)</td>
<td>61.4 ± 7.0 (64)</td>
<td>2.25 ± 1.08 (2.48)^4</td>
</tr>
<tr>
<td>Amberley reference group</td>
<td>415</td>
<td>43.9 ± 7.8 (43.4)</td>
<td>61.4 ± 16.8 (68)</td>
<td>2.11 ± 1.11 (2.08)</td>
</tr>
<tr>
<td>Richmond reference group</td>
<td>530</td>
<td>44.8 ± 8.0 (44.3)</td>
<td>60.7 ± 16.9 (67)</td>
<td>2.21 ± 1.06 (2.20)</td>
</tr>
</tbody>
</table>

* $x = \log((\text{max} + 1) - y) –$ because of the transformation, the scale direction is reversed, i.e., higher values indicate worse outcomes.

† Compared with Amberley study group, $P < 0.0001$.

‡ Compared with Richmond study group, $P < 0.0001$.

§ Compared with methadone study group, $P = 0.0479$.

**Table 3** IIEF domain scores for men with sexual partners

<table>
<thead>
<tr>
<th>IIEF/IIEF domain scores</th>
<th>Methadone N = 53</th>
<th>Buprenorphine N = 14</th>
<th>Maximum possible score</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIEF total mean ± SD (median, range)</td>
<td>50.4 ± 18.2 (57; 6–73)</td>
<td>61.4 ± 10.8 (63.8; 32–74)</td>
<td>75</td>
</tr>
<tr>
<td>Erectile function mean ± SD (median, range)</td>
<td>22.1 ± 8.5 (25; 1–30)</td>
<td>26.6 ± 3.6 (29; 11–30)</td>
<td>30</td>
</tr>
<tr>
<td>Intercourse satisfaction mean ± SD (median, range)</td>
<td>8.7 ± 3.9 (9; 0–15)</td>
<td>12.1 ± 2.0 (12.5; 8–15)</td>
<td>15</td>
</tr>
<tr>
<td>Orgasmic function mean ± SD (median, range)</td>
<td>7.1 ± 3.4 (8; 0–10)</td>
<td>8.2 ± 1.9 (9; 4–10)</td>
<td>10</td>
</tr>
<tr>
<td>Sexual desire mean ± SD (median, range)</td>
<td>5.9 ± 1.9 (6; 2–10)</td>
<td>7.1 ± 1.6 (7.5; 4–9)</td>
<td>10</td>
</tr>
<tr>
<td>Overall satisfaction mean ± SD (median, range)</td>
<td>6.7 ± 2.4 (7; 2–10)</td>
<td>7.4 ± 1.7 (8; 3–18)</td>
<td>10</td>
</tr>
</tbody>
</table>

IIEF = International Index of Erectile Function.

**Table 4** Regression models after backward stepwise regression for IIEF total score and ED domain (partnered men only)

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SE</th>
<th>$t$</th>
<th>$P &gt; t$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIEF total score (transformed), partnered men N = 67; $r^2 = 0.337$</td>
<td>0.0234</td>
<td>0.0077</td>
<td>3.03</td>
<td>0.004</td>
</tr>
<tr>
<td>TT</td>
<td>0.0193</td>
<td>0.0059</td>
<td>-3.28</td>
<td>0.002</td>
</tr>
<tr>
<td>BDI</td>
<td>-0.0168</td>
<td>0.0075</td>
<td>-2.23</td>
<td>0.029</td>
</tr>
<tr>
<td>Constant</td>
<td>4.449</td>
<td>0.341</td>
<td>13.03</td>
<td>0.000</td>
</tr>
</tbody>
</table>

EF domain (transformed), partnered men N = 67; $r^2 = 0.317$

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SE</th>
<th>$t$</th>
<th>$P &gt; t$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TT</td>
<td>0.0067</td>
<td>0.0100</td>
<td>2.66</td>
<td>0.010</td>
</tr>
<tr>
<td>BDI</td>
<td>-0.0034</td>
<td>0.0077</td>
<td>-3.06</td>
<td>0.003</td>
</tr>
<tr>
<td>Age</td>
<td>-0.0239</td>
<td>0.0098</td>
<td>-2.45</td>
<td>0.017</td>
</tr>
<tr>
<td>Constant</td>
<td>28.602</td>
<td>3.763</td>
<td>7.60</td>
<td>0.000</td>
</tr>
</tbody>
</table>

IIEF = International Index of Erectile Function; ED = erectile function; TT = total testosterone; BDI = Beck Depression Inventory.
MMT, but not BMT, had significantly lower IIEF scores compared with community reference groups. Prevalence data presented here relate to ED based on the EF domain. An estimated 53% of partnered men receiving MMT had some degree of ED, more than double the prevalence reported in two large Australian reference groups, and 22.6% had moderate-severe ED. Although it was not possible to determine the prevalence of ED in the men without sexual partners, their lower IIEF desire domain scores and lower levels of recent sexual activity suggest that prevalence of sexual dysfunction is higher in this group than for partnered men.

The IIEF is validated as a measure of EF and does not measure global sexual dysfunction in men as a construct. Nonetheless, the high prevalence of ED in the present study appears to contrast with a previously reported 14% prevalence of global sexual dysfunction in 92 men receiving MMT [11]. Population prevalence data for ED in men vary enormously, reflecting sampling, definition and methodology, and possibly cultural factors. Where an age breakdown has been given, reported prevalence is substantially lower in younger men (20–30 years, 30–40 years, and 40–50 years groups) than older men [22,23].

International Index of Erectile Function scores and prevalence of ED did not differ between men receiving buprenorphine and community reference groups, consistent with the finding of Bliesener et al. that buprenorphine, unlike methadone, is not associated with sexual dysfunction [9]. However, it is possible that the somewhat older mean age of the IIEF reference groups may have obscured a real difference from study group men on buprenorphine. Further, methadone- and buprenorphine-treated men in the present study differed in several ways, including duration of treatment, employment status, alcohol, and benzodiazepine use and may have differed in other ways not controlled for in the multivariate analysis. In the study practice, buprenorphine is commonly used in patients with lower opioid tolerance, and in those reducing their doses; methadone in patients with heavy or persisting heroin use, or with chronic pain. A randomized study might be the only situation where methadone and buprenorphine on sexual function might be mediated by their effects on testosterone, as suggested by Bliesener et al. [9]. However, this conclusion was not supported in the present study when opioid medication was substituted for TT in a cross-sectional study wide interindividual differences in methadone metabolism and tolerance might obscure a methadone dose relationship to sexual function in individuals, which would be revealed in a longitudinal study. Methadone dose reductions in any one individual may lead to normalization of sexual function, and this accords anecdotally with our clinical experience.

International Index of Erectile Function and EF domain for partnered men were significantly associated with lower TT, which is consistent with the association of sexual dysfunction with hypogonadism from other causes. Hypogonadism is clearly associated with hypoactive sexual desire, and while in animals testosterone has direct effects on erectile tissue, its link with ED in humans is less clear [25].

On univariate analysis, TT accounted for only 16% of IIEF variance and 15% of EF variance, and this may give an indication of the limitations of androgen replacement as treatment of ED in this setting. However, the use of single blood samples in this study may not have captured the full strength of the association of TT with EF, owing to variability of androgen secretion [13,25]. Australian guidelines recommend treatment for hypogonadism be based on no less than two morning blood samples [26].

Similarly to the present study, depression was found to be associated with global sexual dysfunction in MMT and with ED in the Massachusetts Male Aging Study [11,27]. The etiological direction of the association between sexual dysfunction and depression is unclear. They may form a vicious cycle. Given the small number of men taking antidepressants in this study, their possible contribution to ED could not be evaluated. On the other hand, this gives a clearer idea of the association of untreated depression with ED.

Etiology of Sexual Dysfunction

Although the treatment variable was close to significance ($P = 0.075$) in the univariate regression for total IIEF, it dropped out in multivariate analysis. Differing effects of methadone and buprenorphine on sexual function might be mediated by their effects on testosterone, as suggested by Bliesener et al. [9]. However, this conclusion was not supported in the present study when opioid medication was substituted for TT in the multivariate model for total IIEF and EF domain—opioid medication was not significant. It is possible that opioids also alter sexual function in other ways than by causing hormonal changes [1,24].

There was no methadone (or buprenorphine) dose relationship to total IIEF or EF domain. This accords with the majority of studies of methadone dose relationship to sexual dysfunction, with the exception of orgasmic dysfunction [11]. However, in a cross-sectional study wide interindividual differences in methadone metabolism and tolerance might obscure a methadone dose relationship to sexual function in individuals, which would be revealed in a longitudinal study. Methadone dose reductions in any one individual may lead to normalization of sexual function, and this accords anecdotally with our clinical experience.

International Index of Erectile Function and EF domain for partnered men were significantly associated with lower TT, which is consistent with the association of sexual dysfunction with hypogonadism from other causes. Hypogonadism is clearly associated with hypoactive sexual desire, and while in animals testosterone has direct effects on erectile tissue, its link with ED in humans is less clear [25].

On univariate analysis, TT accounted for only 16% of IIEF variance and 15% of EF variance, and this may give an indication of the limitations of androgen replacement as treatment of ED in this setting. However, the use of single blood samples in this study may not have captured the full strength of the association of TT with EF, owing to variability of androgen secretion [13,25]. Australian guidelines recommend treatment for hypogonadism be based on no less than two morning blood samples [26].

Similarly to the present study, depression was found to be associated with global sexual dysfunction in MMT and with ED in the Massachusetts Male Aging Study [11,27]. The etiological direction of the association between sexual dysfunction and depression is unclear. They may form a vicious cycle. Given the small number of men taking antidepressants in this study, their possible contribution to ED could not be evaluated. On the other hand, this gives a clearer idea of the association of untreated depression with ED.
Consistent with multivariate modeling for total IIEF and EF domain scores for men with partners, TT and BDI were also associated with sexual desire domain and erection confidence scores in the entire patient group, further supporting the importance of these factors in relation to sexual function in this setting.

Final multivariate models including age, TT, and BDI explained only 34% of IIEF variance and 32% of EF domain variance, suggesting the possible importance of factors not included in the analysis, which need to be explored in further studies. While the impact of anxiety disorders on sexual dysfunction has been little studied, personality disorders are associated with high rates of sexual dysfunction, while self-reported sexual problems were reported as equally prevalent in a general psychiatry, an alcohol misuse, and a substance misuse clinic [28], suggesting possible commonalities among these settings.

Hyperprolactinemia was uncommon, suggesting that bromocriptine should not be used for sexual dysfunction in opioid-treated men on the assumption of hyperprolactinemia [29]. Further, prolactin was not associated with IIEF in the present study.

Study Limitations and Strengths

The main study limitation was the number of participants having no sexual partners, preventing derivation of full IIEF scores for these men. While 80.5% of the male clinic population participated in this study, 12.5% were unwilling or unable to participate. This and the semiprivate nature of the practice may impact on the study’s generalizability. However, sociodemographic factors in the study population are similar to the broader opiate replacement therapy population in Australia [17].

The older mean age of the IIEF reference groups may have obscured the extent of differences from study group men, especially those on buprenorphine. Nevertheless, there is a clear difference between BMT and MMT groups. Nineteen buprenorphine-treated men participated in the study, of whom 14 had sexual partners, a modest addition to the 17 cases previously reported in the literature related to sexual dysfunction [9].

Limitations of the use of the IIEF should be mentioned: as a validated measure of EF, it cannot be asserted to measure global sexual dysfunction, or specific dysfunctions including orgasmic dysfunction and hypoactive sexual desire, which warrant further study in this setting. Against the background of use of unvalidated (often single-question) measures in most of the previously published literature on opioid-related sexual dysfunction, we chose to make limited use of the sexual desire domain and erectile confidence questions scores to cast some light on sexual dysfunction in men without partners, and further to test the associations of TT and BDI with sexual function. However, it is acknowledged that these are not validated instruments in themselves and are not intended independently to evaluate sexual desire and erectile confidence per se.

Strengths of this study include: the availability of large community reference groups for the IIEF; in analyzing a large number of possible factors for association with the outcome measure; the wide range of opioid doses in the study group; and the substantial cross-section of men from a single opioid replacement treatment setting allowing a robust estimation of prevalence of ED.

Clinical Implications and Recommendations

Hanbury et al. found that 10 of 17 men with sexual dysfunction in MMT had not raised the issue out of embarrassment rather than for want of concern [6]. In view of the high prevalence of ED identified in this study, men receiving opioid replacement, especially MMT, should routinely be asked about sexual dysfunction. The possible contributing roles of hypogonadism and depression should be considered where ED is identified.

Buprenorphine may be less likely than methadone to cause sexual dysfunction, and transfer from methadone to buprenorphine is one therapeutic option where sexual dysfunction is identified, as suggested by Bliesener et al. [9]. However, transfer from higher-dose methadone may require prior dose reductions. Despite the absence of a methadone dose relationship to ED in the present cross-sectional study, it is possible that methadone dose reductions may lead to normalization of sexual function. The possible benefits of dose reductions need to be weighed against the risk of continuing heroin use. Owing to the wide interindividual variation in methadone metabolism and tolerance, a wide range of doses required for optimum therapeutic effect [18]. There is little evidence that MMT causes more sexual dysfunction than heroin use, and some evidence of the reverse [2–5].

The modest contribution of testosterone to variance in the IIEF and EF in the present study should be borne in mind in deciding on androgen replacement treatment for ED in men receiving opioid replacement treatment. Where ED does not con-
stitute a symptom, owing to hypoactive sexual desire, it may not need treatment. Where ED is symptomatic, “erectile function is more likely to improve with testosterone therapy in patients with severe degrees of hypogonadism” [25].

A challenge for future studies of sexual dysfunction in opioid-treated men will be to assess the potential benefits of dose reduction, androgen replacement, treatment of depression, and choice of opioid. Finally, these results emphasize the need for similar studies in opioid-treated women.

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References


