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Sexual Dysfunction in Men Receiving Methadone Maintenance Treatment: Clinical History and Psychobiological Correlates

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Key Words
Methadone · Sexual dysfunctions · Childhood neglect · Psychiatric comorbidity · Prolactin · Testosterone · HPG axis

Abstract
Abstract: A variety of studies evidenced a relationship between drug use disorders and sexual dysfunction. In particular, heroin and opioid agonist medications to treat heroin dependence have been found to be associated with erectile dysfunction and reduced libido. Controversial findings also indicate the possibility of factors other than the pharmacological effects of opioid drugs concurring to sexual dysfunction. With the present study, we investigated the link between sexual dysfunction and long-term exposure to opioid receptor stimulation (heroin dependence, methadone maintenance treatment, methadone dosage), the potentially related hormonal changes reflecting hypothalamus-pituitary-gonadal axis function and prolactin (PRL) pituitary release, the role of adverse childhood experiences in the clinical history and the concomitant symptoms of comorbid mental health disorders in contributing to sexual problems. Forty male patients participating in a long-term methadone treatment program were included in the present study and compared with 40 healthy control subjects who never used drugs nor abused alcohol. All patients and controls were submitted to the Arizona Sexual Experiences Scale (ASEX), Child Experiences of Care and Abuse-Questionnaire (CECA-Q) and the Symptom Check List-90 Scale. A blood sample for testosterone and PRL assays was collected. Methadone dosages were recorded among heroin-dependent patients on maintenance treatment. Methadone patients scored significantly higher than controls on the 5-item rating ASEX scale, on CECA-Q and on Symptoms Check List 90 (SCL 90) scale. Testosterone plasma levels were significantly lower and PRL levels significantly higher in methadone patients with respect to the healthy control group. ASEX scores reflecting sexual dysfunction were directly and significantly correlated with CECA-Q neglect scores and SCL 90 psychiatric symptoms total score. The linear regression model, when applied

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only to addicted patients, showed that methadone dosages were not significantly correlated with sexual dysfunction scores except for 'erectile dysfunction', for which an inverse association was evidenced. Testosterone values showed a significant inverse correlation with ASEX sexual dysfunction scores, CECA-Q neglect scores and psychiatric symptom at SCL 90 among methadone patients. PRL levels were directly and significantly correlated with sexual dysfunction scores, psychiatric symptoms at SCL 90 and CECA-Q neglect scores. Both testosterone and PRL did not correlate with methadone dosages. The present findings appear to support the view of childhood adversities and comorbid psychiatric symptoms contributing to sexual dysfunction and related hormonal changes among methadone patients, challenging the assumption that attributes sexual problems entirely to the direct pharmacological effects of opioid agonist medications.

Introduction

A variety of studies have considered the sexual dysfunction related to substance use disorders [1, 2]. Although some drugs can initially increase sexual response, particularly in those with previous sexual problems, the chronic use of substances tends to deteriorate all stages of sexual function in both male and female drug users [3–5]. In line with this evidence, a very high prevalence of sexual dysfunction was recently reported in association with substance use disorders in a Brazilian sample, with a significant correlation between sexual problems and the severity of drug use [6].

In general, male drug users were found to be prone to erectile dysfunction, decreased sexual desire and increased ejaculation latency, with erectile dysfunction and decreased libido most commonly seen in heroin users [7]. Accordingly, in men seeking treatment for opioid dependence, the prevalence of sexual dysfunction was significantly higher in comparison with healthy control subjects [8]. In association with the clinical evidence of sexual dysfunction, impaired hypothalamus-pituitary-gonadal (HPG) axis and increased prolactin (PRL) levels have been found in patients exposed to long-lasting opioid receptor stimulation [5, 9–11].

Until now, there are controversial findings concerning the possible role of the opioid medications utilized in the treatment of heroin dependence as related to sexual dysfunctions. On one side, the rate of heroin-dependent patients suffering from hypo-sexuality and erectile dysfunction was reported to have significantly increased after methadone maintenance treatment with respect to the prevalence measured before opioid substitution therapy [12, 13]. On the other hand, in a more recent study, Zhang et al. [14] found a decrease in the severity of sexual dysfunction in association with methadone maintenance initiation. Moreover, in this study, methadone dose and duration of methadone treatment were not found to be associated with sexual dysfunction, casting doubts upon a direct negative effect of the opioid agonist medications on the sexual function.

Supporting the assumption of a close link between opioid receptor stimulation and sexual problems, additional evidence has shown that the prevalence of sexual dysfunction was higher among the patients treated with methadone compared with those under buprenorphine maintenance [15], possibly indicating that the action of the partial opioid agonist, buprenorphine, would less severely affect the sexual function with respect to that exerted by full agonist medication.

To increase the complexity of the interpretation of existing data in this field, a high prevalence of common dysfunctions, such as premature ejaculation, erectile dysfunction and reduced desire, have been reported in heroin-dependent patients during opioid receptor antagonists treatment with naltrexone [16], once again challenging the simplistic view of a direct pharmacological influence of the opioid system on the sexual response. Accordingly, another research group found that sexual functioning does not improve when drug use is stopped [17], further suggesting the possibility of factors other than the pharmacological effects of drugs contributing to sexual dysfunction.

Moreover, both psychological and social factors have been associated with sexual dysfunction in patients treated with opioid agonist medications [18], and more recently, a meta-analysis study demonstrated that the factors associated with sexual dysfunction among men on methadone treatment include age, hormone levels, duration of treatment, methadone dose, medical status, psychiatric illness and familial status, indicating that a complex etiology, and not a single pharmacological cause, may underlie the sexual problems in these patients [19].

In line with this view, users of controlled psycho-active drugs for non-medical purposes reported being affected by sexual dysfunction prior to drug use initiation, claiming – in a large percentage – that sexual dysfunction influenced their decision to start taking drugs [20, 21]. In this regard, adolescents experiencing elevated levels of negative affect attributable to early sexual maturation

have been found at greater risk for substance use within the next year [22, 23].

Sexual behavior problems and substance use disorders may share common risk/susceptibility factors. In particular, adverse childhood experiences and poor parenting have been repeatedly demonstrated to be associated with substance abuse and risky personality traits in the adults [24–27] and could also negatively influence sexual function. To this purpose, disrupted childhood attachment was commonly found in a sample of men with erectile dysfunction, and this reported association with significant differences in their clinical profile, including an earlier onset, a lower likelihood of being married and higher rates of performance anxiety [28]. Childhood adversities such as sexual abuse were identified as a likely factor in the development of sexual dysfunction in adults [29]. The same seems to be true for hormonal changes, with HPG axis and hypothalamus-pituitary-adrenal axis covariation, also attributable to aversive parenting [30], childhood adversities and related psychological problems [31].

The aim of the present study was to verify whether sexual dysfunction, and commonly related hormonal changes, in heroin-dependent patients treated with methadone were associated to (1) long-term opioid receptor stimulation and, in specific, to the exposure to methadone or (2) childhood adversities, in particular, emotional neglect and (3) symptoms of comorbid mental health disorders.

Our hypothesis was that while long-term exposure to heroin and opioid medications contributed toward worsening of sexual problems and affected the HPG axis, a significant component of the sexual dysfunction among heroin users would be attributable to a vulnerability condition carried by the risk population. To this purpose, sexual dysfunction measures and associated hormonal changes in heroin-dependent patients treated with methadone would correlate more significantly with childhood adversities and comorbid psychiatric symptoms scores than with methadone dosage per se, demonstrating that sexual function is influenced by a complex interaction of factors throughout the clinical history of these patients.

To this end, we included in the study, 40 male heroin-dependent patients on methadone maintenance therapy who volunteered for the study and 40 male healthy control subjects to investigate sexual dysfunction (Arizona Sexual Experiences Scale; ASEX), testosterone and PRL plasma levels, psychiatric symptoms at Symptoms Check List 1990 (SCL 90) and adverse childhood experiences retrospective perception with Child Experience of Care and Abuse – Questionnaire (CECA-Q).

Methods

Subjects

The study was conducted in 2 separate addiction services centers (Servizi Tossicodipendenze – Ser.T Parma) of the Italian public health system, between January 2010 and December 2012. The interventions, policies and procedures in each center were similar, and the accessibility threshold was the same across both centers.

Addiction Services in Italy provide outpatient treatment programs with a variety of therapeutic and rehabilitative strategies; methadone, buprenorphine and naltrexone are administered in association with possible psychosocial interventions, such as psychotherapy, family therapy, group therapy, social support and medications for psychiatric comorbidity. The 2 centers selected for the present study did not differ in the psychosocial treatment protocols associated with methadone, staff dimensions or admission criteria. The majority of patients in the Italian Addiction Services are dependent on heroin, although interventions are also available for patients demonstrating dependence on cannabis, cocaine and alcohol. Patients are routinely evaluated using a self-report and observer-rated questionnaire focused on addiction history, and each patient receives a psychiatric diagnostic screening. No exclusion criteria are applied to patients in the public health system. Patients who fail to respond to interventions such as methadone, and continue to inject heroin, are not dismissed by these centers. A detailed history of patients is obtained from previous drug addiction centers.

In the present study, 40 male patients, of all eligible patients referred for long-term methadone treatment, completed the necessary period of stabilization on a methadone maintenance program. Each of the 2 centers recruited 20 patients willing to participate in the study, remain in treatment for at least 12 months (retention), maintain negative urines and be exposed only to methadone. To obtain a sample of 40 patients, 58 patients were interviewed and 55 recruited. Only 3 patients did not choose to participate in the study. Out of 55 patients, 4 patients did not maintain the methadone program for 12 full months and dropped out earlier relapsing to street heroin; 9 patients remained in treatment but were unable to stop injecting heroin or using cocaine in the 12 months of methadone program; 3 of the 9 patients unable to stop using heroin or cocaine were also prescribed psychotropic medications; 1 patient was affected by a first psychotic episode and hospitalized, and 1 patient was detained for previous legal problems.

In line with the inclusion criteria applied for the recruitment of patients in the study, the participants were required to be heroin-dependent for at least 3 years prior to enrolling in methadone maintenance. Prior daily intake of heroin ranged from 1.5 to 3.0 g of street heroin. All the patients included in the study reported having occasionally abused alcohol or other illicit drugs in the past.

All 55 patients recruited for the study had positive urinalysis for heroin use at the beginning of the treatment program (first days), and the 40 patients who were included in the final study sample showed negative urinalysis for heroin, cannabis, amphetamines and cocaine for the 12 months of methadone maintenance treatment.

Additional exclusion criteria included severe chronic liver illness (with transaminases >60 U/l and gamma-globulins >21%), renal disorder (creatinine clearance 100–120 mg/l/min), other extremely severe chronic medical disorders, recent significant weight loss or obesity (possibly interfering with hormonal measures or

expressing acute illness), endocrine diseases, severe mental health challenges such as schizophrenia and bipolar disorders. Patients who had been prescribed psychotropic medication, other than methadone, were also excluded.

In comparison with the patients on methadone, 40 healthy male controls, matched for age, who were selected from the staff of the hospital or blood donors, never having used illicit drugs or abused alcohol, were included in the study and submitted to the same psychosocial and biological tests.

Patients and control subjects gave informed consent for participation in the observational study, which was approved by the Public Health System ethical committee. Patients were not paid for their participation. Study procedures did not interfere with the daily protocols of the centers.

The study investigated in both, those patients stabilized on methadone maintenance treatment and healthy control subjects, (1) sexual dysfunction and sexual behavior problems, (2) possible experiences of neglect in early childhood, (3) PRL and testosterone plasma levels and (4) concomitant psychiatric symptoms.

Data Collection Strategy

Patients were required to provide the following information: patient identification, extent of heroin exposure (years), participation in previous treatment(s) (methadone, residential programs, number of detoxification treatments), employment status, highest academic level completed, self-reported quality of interpersonal relationships (whether or not the patient has maintained a relationship with the family of origin or with his/her own family), marital status, legal problems, number of arrests, time in prison and perception of alcohol as a current problem. The same demographic information has been obtained from control subjects.

Psychiatric Assessments

All subjects took part in a structured interview for diagnostic evaluation by a trained psychiatrist who was part of the treatment team, utilizing the Italian version of the Structural Clinical Interview for axis I disorders [32, 33] and adopting the Diagnostic Statistic Manual of the American Psychiatry Association (DSM)-IV, the Italian version of the Structured Interview for DSM IV Personality Disorders for axis II disorders [34, 35].

Diagnostic evaluation was carried out during the week before and immediately after the beginning of methadone treatment. A majority of the patients had had previous contact with the addiction centers, and the current psychiatric evaluation in fact confirmed the previous diagnoses reported in their records. All the patients included in the present study did not meet the complete diagnostic criteria for axis I or axis II disorders. All the patients included in the study did meet the DSM-IV criteria for heroin dependence and tested positive for urine morphine metabolites upon recruitment.

Psychosocial and Biological Tests

The patients have been submitted to psychosocial and biological tests at month 12, following stabilization on the methadone maintenance program.

SCL 90

Both addicted patients and control subjects were submitted to the SCL 90 [36], 1992. SCL 90 total score was taken into account as a measure of concomitant psychiatric symptoms in general. This scale has been commonly utilized in previous studies on subjects affected by addictive disorders to evaluate psychiatric comorbidity [37, 38].

Scale About Sexual Problems

The ASEX (Copyright 1997, Arizona Board of Regents) has been utilized in both patients and controls to measure sexual problems [39]. ASEX is a 5-item rating scale that quantifies sex drive, arousal, penile erection, ability to reach orgasm and satisfaction from orgasm. Possible total scores of ASEX range from 5 to 30, with the higher scores indicating more sexual dysfunction. For each item, the patient indicates a score from 1 to 6 demonstrating the severity of the problem. The questions refer to the last week, to explore possible current sexual problems in both methadone patients and control subjects.

CECA-Q

The possible experiences of neglect and abuse during infancy and adolescence were measured retrospectively utilizing the CECA-Q [40] both in patients and controls. The self-report questionnaire was used to assess lack of parental care (neglect and antipathy), parental physical abuse and sexual abuse from any adult prior to 17 years of age. CECA-Q sub-scales include mother neglect, father neglect, mother antipathy, father antipathy, mother physical abuse, father physical abuse and sexual abuse. The patient therapist relationship allowed staff to also obtain a clinical evaluation of adverse childhood experiences from each patient, demonstrating CECA-Q reliability. Neglect cutoff was considered as scores ≥22.

Endocrine Measures: PRL and Testosterone

For hormonal assays (PRL and testosterone), EDTA-decoagulated blood was drawn through a catheter inserted in a vein 30 min before starting the test (7.30 a.m.) and kept patent by saline infusion. Blood samples (10 ml each) were drawn at 8.00 a.m. (time 0) and 8.30 a.m. (time 30). Previous evaluations of 2 basal blood samples, 30 min from one another, evidenced that the second baseline hormonal value was not influenced by IV insertion [41, 42], suggesting that the emotional state had not significantly changed 30 min after insertion: the catheter was not perceived as a stressful stimulus at time 0 (8.00 a.m.).

Blood samples were immediately centrifuged in the cold and the plasma frozen at –80°C until assayed. PRL and testosterone values presented in the study were the average of the 2 values obtained in the 2 basal measures: hormonal values were presented as the average of 2 samples to increase the reliability of the measures, taking into account that only slight non-significant decreases related to circadian rhythm were evidenced between 8.00 and 8.30 a.m. PRL and testosterone plasma concentrations were measured utilizing a full automatic system. The plasma concentration of PRL and testosterone were expressed as ng/ml and ng/dl, respectively. The study was limited to baseline PRL and testosterone levels due to the unwillingness of subjects to submit to multiple blood samples.

Toxicological Analyses

Urine samples were collected during the methadone treatment once a week in a random order and the day before the experiment (ASEX, CECA-Q, SCL 90, blood sample) from all the patients on methadone. Controls were also submitted to urinalysis the day before psychosocial and hormonal tests. Metabolites for morphine, cocaine, amphetamines, cannabis, benzodiazepines, barbiturates, methadone and alcohol were screened.

Methadone Dosage

Methadone mean dosage at the time of the study (month 12) was 87.9 ± 26.6 mg (range 50–150 mg).

Statistical Methods

On account of the lack of normality assumptions for some of the variables within groups, the non-parametric Mann–Whitney U test was used to compare the groups of control and addicted subjects. For the same reason, correlation between variables was tested using Spearman's rho, as this statistic measure is less sensitive to non-normality and presence of outliers then the normal parametric Pearson correlation. To evaluate the role of methadone exposure, hormone levels, SCL scores and neglect scores on sexual dysfunctions, a nested regression analysis was adopted. Methadone exposure consists of a categorical dichotomous variable in which healthy subjects (reference category) are contrasted to methadone patients. The nested analysis determines not only the statistical significance of single explanatory variable, but also the increase in R^2 due to the inclusion of such variables (or groups of variables) in the model. Change in R^2 is tested by means of F test. Three nested models have been estimated; the first model consists of the sole heroin exposure variable, SCL scores are then added in the second step, while neglect scores are the last variable to be included. An analysis of multicollinearity among explanatory variables was carried out before estimating nested regression models. This procedure allows highlighting redundant (collinear) variables that might be responsible for biasing the results by inflating standard errors, thereby making regression coefficients more unstable and not significant. To this purpose, variance inflation factor procedure was applied, which measures how much the variance of a single coefficient is inflated due to collinearity with the other explanatory variables included in the regression. Moreover, effect sizes have been calculated for each of the final models in every nested analysis using Cohen's f^2, which is an index closely associated to R^2 through the relation $f^2 = R^2/(1 - R^2)$. According to Cohen's indications, large effect size is present when $f^2 > 0.35$. This index was then used to perform post-hoc power analysis on the overall R^2 deviation from zero, although some researchers have cast some doubts over the usefulness of such an approach [42].

Finally, association between methadone dosage and sexual dysfunctions was tested on methadone patients only, running a simple linear regression model for each of the 5 sexual dysfunctions considered controlling also for SCL 90 scores and neglect scores (CECA-NM and CECA-NF).

For each regression model, the assumption of normality distribution of residuals has been evaluated and confirmed. In any case, Huber–White robust standard errors were used in regressive models to minimize the effects and flaws associated to non-normality and heteroscedasticity. Statistical significance was always calculated as $p < 0.05$.

Calculations and statistical analyses were performed using the Statistical Package STATA 11.2.

Results

In table 1, demographic data have been reported for both patients and controls. No differences were evidenced in age, rate of married subjects, quality of interpersonal relationships or schooling level. The rates of unemployment and legal problems were higher among heroin users in comparison with controls.

Table 1. Socio demographic characteristics of the sample

	Heroin addicted	Controls
Age	34.5	35.8
Married, %	50	57.5
Good interpersonal realtionships, %	70	77.5
Secondary school diploma or university degree, %	42.5	47.5
Employed, %	52.5	87.5
Legal problems, %	75	5

Table 2 shows the average scores of ASEX, SCL 90, CECA-Q neglect and the average values of testosterone and PRL.

Sexual Dysfunction

Methadone patients scored significantly higher than controls on the 5-item rating ASEX scales that quantifies sex drive ($z = -2.907$, $p = 0.004$), arousal ($z = -2.751$, $p = 0.006$), penile erection ($z = -2.853$, $p = 0.004$), ability to reach orgasm ($z = -3.333$, $p = 0.001$) and satisfaction from orgasm ($z = -3.059$, $p = 0.002$).

Psychometric Results

Total SCL 90 scores were significantly higher among methadone patients than in the healthy control subjects ($z = -7.295$, $p < 0.001$).

CECA-Q values showed significantly higher levels of mother/father neglect (respectively $z = -6.301$, $p < 0.001$ and $z = -5.629$, $p < 0.001$) and antipathy (respectively $z = -4.611$, $p < 0.001$ and $z = -5.944$, $p < 0.001$) among methadone patients in comparison to control subjects.

Endocrine Measures

Testosterone plasma levels were significantly lower among drug-dependent patients than those measured in normal controls ($z = 3.763$, $p < 0.001$). PRL basal levels were significantly higher in heroin-dependent patients on methadone maintenance in comparison with those evidenced in healthy controls ($z = -5.818$, $p < 0.001$).

Correlations

In tables 3 and 4, Spearman's correlation coefficients (rho) are shown for the 2 groups of methadone patients and control subjects. Testosterone values showed a significant inverse correlation with ASEX sexual dysfunc-

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Table 2. Average scores of ASEX, SCL 90, CECA-Q neglect and average values of testosterone and PRL for both groups

Variables	Controls			Methadone patients			Mann–Whitney test	
	mean	SD	median	mean	SD	median	U	p value
Sexdrive	1.70	1.02	1.0	2.48	1.41	2.0	–2.970	0.004
Arousal	1.73	1.13	1.0	2.45	1.40	2.0	–2.751	0.006
Erection	1.68	0.86	1.0	2.65	1.58	2.0	–2.853	0.004
Easy orgasm	1.98	0.97	2.0	2.90	1.28	3.0	–3.333	0.001
Satisfactory orgasm	1.73	0.96	1.0	2.80	1.68	2.0	–3.059	0.002
CECA-AM	9.73	1.43	10.0	12.10	2.28	12.0	–4.611	<0.001
CECA-AF	9.35	1.63	9.0	12.38	2.06	12.0	–5.944	<0.001
CECA-NM	8.90	1.48	9.0	12.48	2.47	12.0	–6.301	<0.001
CECA-NF	9.03	1.82	9.0	12.43	2.42	12.0	–5.629	<0.001
SCL 90	0.81	0.56	0.6	2.92	1.07	2.8	–7.295	<0.001
PRL	6.33	3.80	5.0	14.23	6.50	12.5	–5.818	<0.001
Testosterone	576.65	184.61	565.5	419.13	117.08	422.0	3.763	<0.001

Table 3. Spearman's correlation coefficients. Methadone patients

	PRL	Testosterone	Sex drive	Arousal	Erection	Easy orgasm	Satisfactory orgasm	SCL 90	CECA-AM	CECA-AF	CECA-NM	CECA-NF	Methadone
PRL	1.000												
Testosterone	**–0.833**	1.000											
Sex drive	**0.607**	**–0.727**	1.000										
Arousal	**0.429**	**–0.565**	**0.710**	1.000									
Erection	**0.645**	**–0.645**	**0.756**	**0.745**	1.000								
Easy orgasm	**0.472**	**–0.574**	**0.766**	**0.589**	**0.732**	1.000							
Satisfactory orgasm	**0.608**	**–0.610**	**0.697**	**0.588**	**0.797**	**0.811**	1.000						
SCL 90	**0.774**	**–0.746**	**0.625**	**0.591**	**0.623**	**0.529**	**0.620**	1.000					
CECA-AM	**0.662**	**–0.528**	**0.557**	**0.433**	**0.623**	**0.443**	**0.558**	**0.577**	1.000				
CECA-AF	**0.582**	**–0.487**	**0.550**	**0.413**	**0.729**	**0.448**	**0.562**	**0.470**	**0.775**	1.000			
CECA-NM	**0.698**	**–0.539**	**0.527**	**0.456**	**0.655**	**0.552**	**0.642**	**0.705**	**0.539**	**0.475**	1.000		
CECA-NF	**0.789**	**–0.811**	**0.671**	**0.541**	**0.695**	**0.566**	**0.722**	**0.722**	**0.709**	**0.639**	**0.597**	1.000	
Methadone	0.240	–0.195	0.044	–0.054	–0.118	0.056	–0.002	0.177	0.142	–0.055	0.189	0.127	1.000

Statistically significant coefficients ($p < 0.05$) in bold.

Table 4. Spearman's correlation coefficients. Control subjects

	PRL	Testosterone	Sex drive	Arousal	Erection	Easy orgasm	Satisfactory orgasm	SCL 90	CECA-AM	CECA-AF	CECA-NM	CECA-NF
PRL	1.000											
Testosterone	**–0.439**	1.000										
Sex drive	**0.412**	**–0.499**	1.000									
Arousal	0.293	**–0.749**	**0.609**	1.000								
Erection	0.293	**–0.625**	**0.574**	**0.699**	1.000							
Easy orgasm	0.213	**–0.550**	**0.407**	**0.510**	**0.506**	1.000						
Satisfactory orgasm	**0.359**	**–0.515**	**0.450**	**0.609**	**0.544**	**0.357**	1.000					
SCL 90	**0.459**	**–0.538**	**0.517**	**0.668**	**0.570**	**0.494**	**0.555**	1.000				
CECA-AM	0.187	**–0.396**	0.161	**0.465**	**0.399**	**0.416**	0.292	**0.337**	1.000			
CECA-AF	–0.101	–0.064	–0.164	0.241	0.081	0.216	0.198	0.048	0.142	1.000		
CECA-NM	0.222	**–0.484**	0.278	**0.489**	**0.377**	0.178	**0.363**	**0.429**	0.283	0.261	1.000	
CECA-NF	**0.415**	**–0.458**	**0.419**	**0.507**	**0.312**	0.305	**0.459**	**0.457**	0.191	0.294	**0.416**	1.000

Statistically significant coefficients ($p < 0.05$) in bold.

tion scores, psychiatric symptoms at SCL 90 and CECA-Q neglect scores among methadone patients. In contrast, PRL levels were directly and significantly correlated with sexual dysfunction scores, psychiatric symptoms at SCL 90 and CECA-Q neglect scores. ASEX scores reflecting sexual dysfunction were directly and significantly correlated with psychiatric symptoms at SCL 90 and CECA-Q neglect scores. It is to be noted that no significant association was found between methadone dosage and any of the sexual dysfunction ASEX scores, hormonal levels, CECA-Q scores and SCL scores. The pattern is even more variegated in the control group (table 4). While testosterone is in fact still significantly and inversely correlated with PRL, ASEX scores, CECA-Q scores and SCL 90 scores, PRL does not show any significant correlation with either CECA-Q scores or elements of sexual dysfunction. Even the correlation pattern between ASEX scores and CECA-Q scores is more complicated in the control group than in the group of methadone patients.

Nested Regression Analysis

A preliminary analysis of multicollinearity have led to the exclusion of hormone levels, which presented, especially PRL, high values (over 6) of the variance inflation factor. This is the consequence of the very high correlation between hormone levels and both SCL 90 scores and neglect scores in the group of methadone patients (table 3). For the same reason, only neglect scores were introduced in the models given the very high correlation among CECA-Q scores of neglect and antipathy.

The models shown in table 5 provide results of the nested regression models for the 5 indicators of sexual dysfunctions, namely sex drive, arousal, erection, easy orgasm and satisfying orgasm. The tables show a similar pattern across models. When sexual dysfunction variables are regressed only on methadone exposure, the models provide consistent findings of the positive and significant relationship between methadone treatment and sexual dysfunction scores. The regression coefficients for such a category show an association with sexual dysfunctions 0.7–1.0 points higher than the reference category of healthy individuals. When SCL 90 scores are added to the models, not only does such a variable show significant and positive association with ASEX scores (about 1 point increase in ASEX scores for each unitary increase in SCL scores), but also the explanatory power of each model shows a marked and significant increase. In fact, R^2 increases from values about 0.1 to values very close to 0.5. In addition, the inclusion of SCL scores into models causes a general phenomenon of association reversal between methadone exposure and ASEX scores. In

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Table 5. Effects of methadone, SCL 90 scores and neglect CECA-Q scores on sexual dysfunctions. Nested regression models

	b	RSE	p value	b	RSE	p value	b	RSE	p value
Sex drive									
Controls (ref. cat.)									
Methadone	0.775	0.275	**0.006**	–1.145	0.359	**0.002**	–1.164	0.364	**0.002**
SCL 90 scores				0.911	0.156	**<0.001**	0.509	0.181	**0.006**
CECA-NM							0.097	0.074	0.192
CECA-NF							0.153	0.059	**0.012**
Constant	1.700	0.161	**<0.001**	0.962	0.155	**<0.001**	–0.952	0.643	0.143
R^2	0.092			0.457			0.520		
F (df1, df2)	7.92	1	78	51.70	1	77	4.92	2	75
p value	**0.006**			**<0.001**			**0.006**		
Change in R^2	–			0.365			0.063		
Arousal									
Controls (ref. cat.)									
Methadone	0.725	0.284	**0.013**	–1.302	0.380	**0.001**	–1.310	0.369	**0.001**
SCL 90 scores				0.962	0.151	**<0.001**	0.615	0.214	**0.005**
CECA-NM							0.057	0.084	0.501
CECA-NF							0.158	0.076	**0.043**
Constant	1.725	0.179	**<0.001**	0.946	0.146	**<0.001**	–0.702	0.765	0.362
R^2	0.077			0.466			0.515		
F (df1, df2)	6.51	1	78	56.00	1	77	3.81	2	75
p value	**0.013**			**<0.001**			0.060		
Change in R^2	–			0.389			0.049		
Erection									
Controls (ref. cat.)									
Methadone	0.975	0.284	**0.001**	–1.195	0.341	**0.001**	–1.225	0.331	**<0.001**
SCL 90 scores				1.030	0.127	**<0.001**	0.582	0.181	**0.002**
CECA-NM							0.139	0.070	**0.050**
CECA-NF							0.140	0.068	**0.043**
Constant	1.675	0.136	**<0.001**	0.841	0.135	**<0.001**	–1.297	0.681	0.061
R^2	0.131			0.550			0.618		
F (df1, df2)	11.78	1	78	66.18	1	77	5.37	2	75
p value	**0.001**			**<0.001**			**0.007**		
Change in R^2	–			0.419			0.068		
Easy orgasm									
Controls (ref. cat.)									
Methadone	0.925	0.254	**<0.001**	–0.774	0.349	**0.030**	–0.776	0.364	**0.036**
SCL 90 scores				0.806	0.122	**<0.001**	0.647	0.191	**0.001**
CECA-NM							0.019	0.076	0.800
CECA-NF							0.079	0.059	0.185
Constant	1.975	0.154	**<0.001**	1.322	0.146	**<0.001**	0.568	0.697	0.417
R^2	0.145			0.462			0.475		
F (df1, df2)	13.27	1	78	43.93	1	77	1.02	2	75

Table 5. (continued)

	b	RSE	p value	b	RSE	p value	b	RSE	p value
p value	**0.001**			**<0.001**			0.364		
Change in R^2	–			0.316			0.013		
Satisfactory orgasm									
Controls (ref. cat.)									
Methadone	1.075	0.306	**0.001**	–1.322	0.335	**<0.001**	–1.341	0.326	**<0.001**
SCL 90 scores				1.138	0.122	**<0.001**	0.649	0.178	**0.001**
CECA-NM							0.108	0.060	0.075
CECA-NF							0.195	0.061	**0.002**
Constant	1.725	0.152	**<0.001**	0.804	0.141	**<0.001**	1.520	0.655	**0.023**
R^2	0.136			0.574			0.647		
F (df1, df2)	12.32	1	78	86.84	1	77	7.23	2	75
p value	**0.001**			**<0.001**			**0.001**		
Change in R^2	–			0.437			0.073		

b = Regression coefficient; RSE = robust standard error; ref. cat. = reference category.
F (df1, df2) = F test for overall (model) significance, with degrees of freedom for numerator (df1) and denominator (df2) and p value.
Change in R^2 = Change in R^2 between 2 nested models statistically significant coefficients ($p < 0.05$) in bold.

Table 6. Effect sizes of final regression models

Variables	f^2
Sex drive	1.08
Arousal	1.06
Erection	1.62
Easy orgasm	0.90
Satisfying orgasm	1.83

fact, low-dosage and high-dosage methadone groups now show a negative and significant association with sexual dysfunctions. This apparent paradox is known as 'net suppression' [43, 44], and it occurs because methadone exposure is highly and positively correlated with SCL scores but only weakly and positively with sexual dysfunctions, whilst SCL scores show high correlation with sexual dysfunctions (tables 3 and 4). Thus, methadone exposure has much more in common with the error variance of SCL scores than it does with the error variance of ASEX scores. This implies that, although it accounts for a small amount of variance in the outcome, it functions primarily as a suppressor of the variance in SCL scores that is irrelevant to ASEX scores, thereby improving the predictive utility of SCL scores. In other words, when only methadone exposure is regressed on ASEX scores, the large positive association that emerges is largely the consequence of its strong positive correlation with SCL scores. When this latter variable is finally included in the model, its association with ASEX scores gets reinforced, whilst the association between ASEX scores and methadone exposure, once depurated by its correlation with SCL scores, turns negative.

The third step in the nested procedure concerns the introduction of neglect scores. The addition of mother-neglect and father-neglect scores do not change the sign and intensity of the other regression coefficients significantly but improve the explanatory power significantly in 3 of the 5 models shown in table 5 (sex drive, erection, and satisfying orgasm), while for arousal the change in R^2 is on the edge of statistical significance ($p = 0.06$). As for the single variables, father neglect is found to be significantly and positively associated to sex drive ($b = 0.153$, $p = 0.012$), arousal ($b = 0.158$, $p = 0.043$), erection ($b = 0.140$, $p = 0.043$) and satisfying orgasm ($b = 0.195$, $p = 0.002$). No significant association has been found for easy orgasm ($b = 0.079$, $p = 0.185$). On the other hand, mother neglect emerged as statistically significantly associated to ASEX scores only for erection ($b = 0.139$, $p = 0.050$).

Table 6 shows that each of the final regression models of every nested analysis presents large effect size, always

Table 7. Effect of methadone dosage on sexual dysfunctions

Variables	b	RSE	p value	95% CI	R^2	F (p value)
Sex drive	–0.008	0.007	0.286	–0.022 to 0.007	0.563	9.3 (<0.001)
Arousal	–0.009	0.007	0.235	–0.024 to 0.006	0.479	7.4 (<0.001)
Erection	–0.016	0.006	**0.008**	–0.028 to –0.004	0.709	25.5 (<0.001)
Easy orgasm	–0.006	0.006	0.335	–0.018 to 0.006	0.472	9.3 (<0.001)
Satisfying orgasm	–0.009	0.006	0.100	–0.020 to 0.002	0.694	21.2 (<0.001)

The models control also for SCL 90 scores and neglect scores. Statistically significant coefficients ($p < 0.05$) in bold.

See table 5 for explanation of symbols.

above 1 with the exception of easy orgasm, where $f^2 = 0.90$. They are definitely higher than the threshold proposed by Cohen (0.35). The consequence of such a result is that there is sufficient statistical power (always over 0.95) to detect a significant deviation of overall R^2 from zero.

Finally, the effect of methadone dosage on sexual dysfunctions was tested on the 40 patients under methadone treatment (table 7). The linear regression models show that methadone dosage was not significantly effective in modifying sexual dysfunctions scores except for erection, for which a statistically significant inverse association was found (–0.016, $p = 0.008$), implying that the higher the methadone dosage, the lower were the scores of erection dysfunction.

Discussion

The findings of the present study appear to indicate a significantly higher rate of sexual dysfunction, reduced basal plasma levels of testosterone and increased PRL levels among heroin-dependent patients on methadone maintenance treatment, as compared with healthy controls. Sexual dysfunction scores and hormonal values did not correlate with methadone individual dosages, with the exception of erectile dysfunction, but with childhood neglect scores retrospectively reported by methadone patients and comorbid psychiatric symptoms scores.

Our results do not permit to exclude the role of long-term opioid receptor stimulation and opioid agonist medications as possible factors impacting sexual function and affecting the related hormonal levels. The high prevalence of sexual dysfunction among our methadone patients and the correlation of erectile dysfunction with methadone dosages are consistent with previously reported findings by other research groups concerning the association of opioid receptor stimulation with impaired sexual function [13, 45]. In line with these studies, libido inhibition and decreased sexual pleasure have been described in patients treated with methadone, which was thought to have a stronger inhibition effect on sexual desire than heroin [46]. Accordingly, erectile dysfunction was evidenced in a large rate of heroin-addicted patients, both at the beginning of methadone treatment and during the first months of maintenance therapy [47] and sexual function impairment was found significantly related with duration of treatment and methadone dosage.

On the other side, the evidence gathered by the present study seems to suggest that the sexual dysfunction among methadone patients could also be attributed to a clinical history of adverse childhood experiences, early trauma and poor parenting, all conditions so commonly demonstrated in patients with substance use disorders [25]. To this purpose, sexual dysfunction following trauma exposure has been reported in post-traumatic stress disorders [48] and found associated with disrupted childhood attachment [28]. In line with this previous evidence and our present findings, long-lasting adverse relationship with attachment figures and the perception of neglect have been reported influential to later sexual dysfunction [49, 50]. More recently, cumulative childhood neglect was found associated with delayed development of several pubertal markers [51], with a potential link to consequent forms of sexual dysfunction. Looking from the same perspective, adverse childhood experience scores have been reported to be related to the risk of every negative outcome in the affective, somatic, substance abuse, memory, sexual and aggression-related domains [52].

As a possible consequence of early exposure to stress, comorbid affective and anxiety disorders could be part of a condition of shared vulnerability, underlying the risk for both drug dependence and sexual disturbances/re-

duced libido [53]. In agreement with these data, our present findings demonstrate a significant association between psychiatric comorbidity symptoms, sexual dysfunction and childhood neglect. To underline a potential role of psychiatric comorbidity in the sexual dysfunction of methadone patients, the interference of depressive symptoms and social factors on the relationship between opioid medications and erectile dysfunction was previously suggested by Quaglio et al. [18].

Looking at the hormonal changes evidenced in our study, with low level of testosterone and high levels of PRL directly correlated with sexual dysfunctions, it would be possible to attribute them to the direct effect of opioid receptor stimulation on HPG and pituitary. As indicated by previous findings, the exposure to heroin was thought to exert a depletion effect on testosterone and follicle stimulating hormone levels in just about all the groups studied irrespective of age, amount of heroin intake per day and period of contact with heroin [54]. Similarly, plasma levels of free testosterone were reported to be significantly low [55] and PRL levels significantly high [11, 56] in heroin addicts. Lower levels of testosterone and higher levels of PRL were found among methadone patients also in our study, in comparison with healthy controls, but hormonal values did not correlate with methadone dosages, once again suggesting a more complex mechanism underlying the neuroendocrine changes.

Hormonal changes accompanying sexual dysfunction in the present study were found to be significantly correlated to early stressful conditions, such as neglectful parenting, and total score of comorbid psychiatric symptoms. Accordingly, the association between the symptoms of mental health disorders, psychological distress and the hormonal pattern (lower testosterone) was suggested by other research groups to mediate the negative consequences on sexual function and sexual desire demonstrated in subjects with a diagnosis of depression, anxiety and insomnia [57]. Since the early nineties, hyperprolactinemia has been reported to be significantly associated with paternal deprivation during childhood [30], emotional difficulties and stressful life events [31]. In the same perspective, high cortisol and low testosterone levels during adulthood were found in subjects with early paternal deprivation compared with those of males raised with a resident father, indicating that family environment has significant effects on endocrine responses throughout life histories [58] and on reproductive functioning as a clinical consequence [59].

In line with our hypothesis and our findings among methadone patients, psychological distress in non-addicted subjects was found associated with idiopathic or 'functional' hyperprolactinemia [60], anxiety and hostility at SCL 90 scores being positively correlated to high plasma levels of PRL. Feeling stressed in a sample of subjects without psychiatric disease was also found associated to stress-related hormones (PRL and cortisol) increase, with a clear correspondence between PRL levels and stress subscales scores [61]. Accordingly, lower testosterone levels and higher levels of PRL have been reported in subjects with depression and higher suicidality [62, 63] in post-traumatic stress disorder patients [64] and in soldiers with post-traumatic stress disorder and comorbid major depression [65].

Considering the modest sample size, the great inter-individual variability in response to opioid drugs due to pharmacogenetic reasons [66] and the retrospective evaluation (subjective perception) of parental neglect, our results should be interpreted with caution. In particular, the key limitation of the present study is the impossibility to disentangle the effects of demoralization and stigma on mood and self-image, on current relationships and on recollections of childhood perception. As an alternative interpretation of our findings, opioids would have stimulated PRL release, with resulting reduction in luteinizing hormone and testosterone, and reduced testosterone may have been associated with greater current distress (and sexual dysfunction), not primarily being related to early stressful experiences in the clinical history.

However, the present findings indicate a significant association of childhood adversities and comorbid psychiatric symptoms with sexual dysfunction and related hormonal changes among heroin-dependent patients treated with methadone. In any case, causal relations cannot be established on the basis of these preliminary data obtained with a cross-sectional study design.

The meaningful aspect of these preliminary findings is to underline the complexity of drug use disorders and their treatment, moving from simplistic interpretation focusing only on the pharmacological aspects to a personalized approach that takes into account the entire person, the clinical history and the possible comorbidity. For that reason, sexual dysfunction, commonly reported in heroin-dependent patients on methadone maintenance treatment, does not seem to be related to the mechanistic effects of opioid agonists, but to concurrent individual and environmental factors beyond the drug effects themselves.

If confirmed, this evidence can significantly influence clinical practice, suggesting that health professionals deal with sexual problems of opioid-dependent patients utiliz-

ing a psychological and possibly psychotherapeutic approach and not only a pharmacological one. Further study could better investigate the sexual function in heroin-dependent patients, particularly during methadone treatment, adopting a prospective design to explore the possible sequence of early life stressful conditions, sexual dysfunction and comorbid psychiatric symptoms respect to substance initiation and the onset of substance use disorders.

Disclosure Statement

The authors declare no conflicts of interest.

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