Current Sexual Health Reports (2018) 10:158–168
https://doi.org/10.1007/s11930-018-0160-7

MALE SEXUAL DYSFUNCTION AND DISORDERS (AW PASTUSZAK AND NK GUPTA, SECTION EDITORS)

Opioid-Related Sexual Dysfunction in Men

Catherine T. Nguyen[1] · Justin La[1] · Faysal A. Yafi[1]

Published online: 21 July 2018

Abstract

Purpose of Review Opioids are the cornerstone for pain treatment with significant recent increases in the number of prescriptions. Sexual dysfunction (SD) is a major side effect of opioid therapy. The goal of this review is to examine the current literature on the effects of opioids on male SD (erectile dysfunction [ED], hypogonadism, ejaculatory dysfunction) and infertility.

Recent Findings High prevalence of SD exists in men with opioid use as compared to the general population, with an abundance of evidence suggesting an association between opioid use and ED and hypogonadism. There appears to be a role for testosterone replacement therapy for hypogonadism in men on opioid therapy. Screening for low testosterone levels is recommended in men on opioid therapy with signs and symptoms of androgen deficiency. Data on fertility, ejaculatory, and orgasmic dysfunction are limited.

Summary SD is significantly affected by opioid therapy in men. Data demonstrate the benefits of screening for SD and treatment for hypogonadism.

Keywords Opioid · Sexual dysfunction · Erectile dysfunction · Ejaculatory dysfunction · Premature ejaculation · Opioid induced androgen deficiency (OPIAD)

Introduction

Opioids remain the current cornerstone for the treatment of pain. An estimated 25 million adult Americans suffer daily from pain, and another 23 million suffer from severe recurrent pain, resulting in disability, loss of work productivity, loss of quality of life, and reduced overall health status [1]. The World Health Organization estimates that chronic pain is present in 22% of primary care patients [2]. Furthermore, up to 42% of emergency room visits are related to pain [3]. Opioids can be classified into three classes—opium alkaloids, semi-synthetic, and fully synthetic. Opium alkaloids are compounds naturally occurring in plants and include morphine, codeine, and thebaine. The semi-synthetic opioids are compounds that are created from naturally occurring opiates including hydromorphone, hydrocodone, oxycodone, buprenorphine, and heroin. Fully synthetic opioids include methadone, fentanyl, and tramadol, among others [4].

The poppy plant was first cultivated in 3400 BC by the Sumerians of Mesopotamia. They were used recreationally and for various medical ailments. In the early 1500s, laudanum or a tincture of opium was thought to be created and promoted by Philippus von Hohenheim, a Swiss physician who is often called the "father" of toxicology. Morphine was first isolated from opium in 1804 by German pharmacist Friedrich Serturner and was widely used as a painkiller during the Civil War, causing addiction among soldiers. The discovery of codeine followed in 1830 to replace raw opium for medical purposes. In an attempt to find a less addictive alternative to morphine, heroin was synthesized by chemist Charles R.A. Wright in 1874 and was initially used as an analgesic and cough suppressant. Subsequent searches for less addictive analgesics led to the discovery of methadone in 1939 [5–8].

Although opioids are primarily used for pain control, they are also highly addictive. Chronic use of opioids increases the risk for addiction, and treatment of addiction is often with other synthetic opioids, predominantly methadone and more

This article is part of the Topical Collection on *Male Sexual Dysfunction and Disorders*

✉ Faysal A. Yafi
faysalyafi@gmail.com

[1] Department of Urology, University of California, Irvine, 333 The City Blvd W, Suite 2100, Orange, CA 92868, USA

recently buprenorphine. The use of legal and illegal opioids has risen 10–14 times in the last two decades [9]. Since 2000, there has been a 200% increase in opioid-related (pain relievers and heroin) overdose deaths in the USA [10]. According to the Centers for Disease Control, the age-adjusted rates of death from 2013 to 2014 involving natural and semi-synthetic opioid pain relievers, heroin, and synthetic opioids have increased by 9, 26, and 80%, respectively. Given the increase in opioid use and detrimental sequelae of improper usage, it is important to be cognizant of the various health effects of the opioid epidemic.

One of the most common side effects of opioid use is sexual dysfunction (SD). Male SD is known to negatively impact quality of life [11–14]. SD can be further categorized into erectile dysfunction (ED), hypogonadism, ejaculatory dysfunction, and orgasmic dysfunction. There are many cross-sectional studies demonstrating a high prevalence of SD in men on opioid therapy, and this phenomenon has been corroborated around the world using a variety of scales for quantifying SD [15•, 16•, 17–21, 22•, 23, 24]. However, only a few studies have examined the statistical correlation or causal relationship between opioid use and SD, and currently, there is no guideline for screening, monitoring, or treating opioid-related SD and infertility in men on opioid therapy or with opioid dependence. Additionally, there is limited information on the effects of opioids on orgasmic dysfunction and, therefore, this subcategory of SD was omitted from our review. The goal of this review is to examine the relationship between opioids and SD and infertility in men.

Opioids and Erectile Dysfunction

ED is the inability to achieve or maintain an erection suitable for satisfactory sexual intercourse. The reported prevalence for ED for all ages in the general population is 18–52%. When looking at men on opioid therapy, ED occurs in 21–67% of men 28–49 years old [12, 17, 23, 25–28].

There are several studies examining the relationship between opioids and ED (Table 1). A recent meta-analysis including ten studies consisting of 8829 men on opioid therapy demonstrated that the use of opioids was positively associated with an increased risk of ED (RR 1.96, $P < 0.001$) [16•]. Furthermore, a cross-sectional electronic medical record study on men with chronic back pain demonstrated that long-term opioid use is associated with greater use of medications for ED or testosterone replacement (TRT), compared to patients with no opioid use (OR 1.45, $P < 0.01$) [24].

Two common opioid therapies for chronic pain or opioid dependence include methadone and buprenorphine. The first methadone maintenance therapy program was started in the 1960s with buprenorphine approved for treatment of opioid dependence only in 2002 [37]. Some studies have reported a higher prevalence of ED associated with methadone maintenance therapy (MMT) use as compared to the general opioid-naive population [12, 33, 38] Although the studies for buprenorphine maintenance therapy (BMT) alone are sparse, several studies comparing MMT and BMT have demonstrated that men receiving BMT have a lower prevalence of ED compared to those on MMT [17, 23, 39, 40]. A study in China examining men with heroin addiction showed improvements in erectile function after switching to MMT [34]. In contrast, a recent meta-analysis in Iran showed no change in the prevalence of ED after starting MMT in opioid-addicted men [36]. Major predictive risk factors for ED in opioid users include dosage, older age, concurrent depression, and lack of a sexual partner [12, 23, 30, 31, 33, 41].

The underlying pathophysiology for opioid-induced ED remains unknown. One popular theory is the inhibition of gonadotropin-releasing hormone (GnRH) secretion by opioids. While serum testosterone levels are low in opioid users (meta-analysis of 17 studies with mean difference = −164.78 ng/mL, ($P < 0.0001$)), there is no significant correlation between testosterone level and ED in opioid users [22•, 23, 28, 30, 42, 43]. While numerous studies have shown an association between ED and testosterone levels in the general population, it is worth noting that others have not [44–47].

Opioids and Hypogonadism

Male hypogonadism is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) due to disruption of one or more levels of the hypothalamic-pituitary-gonadal axis [29]. Signs of androgen deficiency may include testicular atrophy, anemia, reduced facial hair growth, infertility, decreases in bone mineral density, and changes in body muscle and fat composition. Hypogonadism has also been associated with the metabolic syndrome [32, 35]. The association between opioids and low testosterone level is well established [22•, 30, 42, 48–50]. Hypogonadism associated with opioid use is referred to as opioid-associated androgen deficiency (OPIAD). The proposed mechanism for OPIAD is through direct inhibition of GnRH release by binding of the opioid to the Mu receptor, which leads to reduced production of luteinizing hormone (LH) and follicle stimulating hormone (FSH) at the level of pituitary, and ultimately testicular testosterone (Fig. 1) [51]. Table 2 summarizes studies examining the relationship between opioid use and hypogonadism.

A recent systematic review and meta-analysis of 17 studies demonstrated a significantly lower level of testosterone in male opioid users by 165 ng/dL ($P < 0.0001$), independent of the type of opioid and frequency of intake [22•]. Compared with short acting (SA) opioids, men on long acting (LA) opioids were more likely to be androgen deficient (57 vs 35%, $P < 0.001$). This

Table 1 Studies examining the relationship between opioid therapy and erectile dysfunction

Study	Design	Subjects	Drugs	Scale	Results
Brown et al. 2005 [28]	Cross-sectional	92	MMT(92)	Nowinski-Lopiccolo Sexual History Form	14% of men on MMT for addiction reported SD. ED, libido or global dysfunction increased with age. Methadone dose significantly correlated with increased orgasmic dysfunction both before and after adjustment for duration of therapy. None of the SD subscales of global dysfunction were associated with T or prolactin levels.
Shiri et al. 2006 Iran [29]	Cross-sectional	312	Opium-addicted men with diabetes (35)	IIEF-5	Prevalence of moderate or complete ED was 85.7% in opium users vs 66.1% in non-users. Opium use is associated with higher risk of ED (OR 2.0 95% CI 1.0–7.4)
Hallinan et al. 2008 Australia [23]	Cross-sectional	103	MMT (84), BMT (19)	IIEF-5, BDI, hormone assays	ED reported in 52.8% of partnered men with addiction on MMT vs 21.4% in BMT group and 24% in healthy reference group. Depression, older age, and lower T levels were associated with lower IIEF and EF domains on multiple regression analysis.
Quaglio et al. 2008 Itlay [17]	Cross-sectional	201	MMT (85), BMT (116)	IIEF-5, Zung depression scale	Subjects on opioid for history of addiction. 24% reported mild to moderate ED, 18% severe ED. Subjects on BMT had less severe ED than subjects on MMT ($P = 0.0135$). Heterosexual subjects and those living with a partner reported less severe ED ($P = 0.0018$), whereas subjects with more depression had more severe ED ($P < 0.001$).
Bang-Ping et al. 2009 Taiwan [27]	Cross-sectional	701 subjects using illicit drugs, 196 control subjects	Heroin, methamphetamine, MDMA (ecstasy)	IIEF-5	ED reported in 36.4% of abusers. The OR of having ED vs controls in mono-users of heroin, amphetamine, and MDMA was 4.8 ($P < 0.05$), 3.2 ($P < 0.05$), 1.4($P > 0.05$), respectively. Decreased sexual desire reported in 38.6% of abusers, most commonly heroin users (46.7%).
Cioe et al. 2010 [30]	Cross-sectional	57	Men on illicit opioids	IIEF-5, hormonal assay	Prevalence of ED is 34%. The ED and non-ED groups had similar mean total testosterone levels (412.8 vs 454.0, $P = 0.5$). There were no significant associations between ED and total testosterone, BMI, baseline BDI, smoking, and opioid of choice or duration of opioid use.
Chen et al. 2012 China [31]	Cross-sectional	74	MMT (74)	IIEF-5, Zung Self Rating Depression Scale, Zung self Rating Anxiety scale	Subject with history of heroin addiction. Slight decrease in prevalence of ED from baseline to month 3 of treatment, not statistically significant. Significant association of dosage and severity of ED at first and second month of follow-up ($P < 0.05$).
Cioe et al. 2013 [32]	Randomized, double-blind, placebo--controlled trial	111 males (17 lost to follow-up)	Heroin (74), oxycodone (28), hydrocodone (13), other (13)	IIEF-5	Compared to baseline, significant improvement in mean erectile function (3.6 points, $P = 0.001$) at 3 months and sexual desire ($P = 0.002$) at both 2- and 3-month assessments. No statistically significant differences in erectile function between those randomized to treatment with an SSRI and those receiving placebo.
Deyo et al. 2013 [24]	Cross-sectional analysis of EMR	11,327	Men with diagnosis of chronic back pain on		Men prescribed medications for ED or TRT were significantly older than those who were not prescribed medications (mean age

Table 1 (continued)

Study	Design	Subjects	Drugs	Scale	Results
	and pharmacy records		MED of various opioids		55.7 vs 48.0 years, $P < 0.01$). Long-term opioid use was associated with greater use of medications for ED or TRT compared to patient with no opioid use (OR 1.45, 95% CI 1.12–1.87, $P < 0.01$); Patients prescribed daily doses of 120 mg morphine equivalent or more had OR 1.58 (95% CI 1.03–2.43). Depressive disorders (OR 1.30, 95% CI 1.06–1.6, $P = 0.01$) and use of sedative-hypnotics (OR 1.30, 95% CI 1.08–1.56, $P = 0.006$) were independently associated with use of medication for ED or TRT.
Nik Jaafar et al. 2013 Malaysia [33]	Cross-sectional	108	Opioid addicts on MMT (108)	IIEF-5, BDI	Rate of ED was 68.5% (mild 36.1%, moderate 22.2%, severe 3.7%) on MMT. Older age, concurrent illicit heroin use, and having older partner were significantly associated with ED.
Zhang et al. 2014 China [34]	Retrospective and cross-sectional	293	MMT (293)	IIEF-5	The median IIEF-5 score of men addicted to heroin after starting MMT was 33 which is significantly higher than prior ($P < 0.0001$). Significant decrease in prevalence for all sexual domains after starting MMT: severe ED from 65.2 to 37.2%, severe orgasmic dysfunction from 70.1 to 39.3%, severe lack of sexual desire from 71.7 to 43.0%, severe lack of intercourse satisfaction from 69.6 to 39.6%, and severe lack of overall satisfaction from 70.0 to 41.0%. On univariate analysis, older age and longer time of heroin use were found to be strong risk factors for sexual dysfunction both before and after initiating MMT.
Yee et al. 2014 [15]	Meta-analysis	16 studies	MMT (236), BMT (186)		Among the four studies comparing MMT and BMT for addiction, the combined OR for SD was significantly higher in the methadone group (OR 4.01, 95% CI, 1.52–10.55, $P = 0.0049$). Eight clinical factors are associated with SD among men receiving opioid substitution treatment: age, hormone assays, duration of treatment, methadone dose, medical status, psychiatric illness, other current substance use and familial status, and methadone vs buprenorphine treatment.
Ajo et al. 2016 Spain [35]	Cross-sectional	120 males	Chronic non-cancer pain on long-term opioids (94 male). Control subjects (26)	IIEF-5	In men on chronic opioids, prevalence of ED was mild 21%, moderate 10%, and severe 69%. Significant correlation between IIEF-EF score and MED was found in patients with SD ($P < 0.008$). Total IIEF and IIEF-EF scores were significantly higher for sexually active men compared to non-sexually active men ($P < 0.05$). Men on tapentadol, oxycodone, or naloxone had lower IIEF-EF scores than men on other opioids ($P = 0.034$ and $P = 0.015$, respectively).
	Meta-analysis	9 studies of men with	MMT	N/A	Prevalence of ED in men on MMT was 77.5%. Comparing pooled sexual

Table 1 (continued)

Study	Design	Subjects	Drugs	Scale	Results
Babakhanian et al. 2017 Iran [36]		heroin addiction			dysfunction scores from before and after starting MMT, sexual desire score increased by 0.16 point, orgasmic dysfunction score decreased by 0.01 point, and erectile dysfunction score increased by 0.11 point. No statistical difference in ED, orgasmic dysfunction, or sexual desire after starting MMT therapy was observed.
Teoh et al. 2017 Malaysia [12]	Cross-sectional	134	MMT (134)	IIEF-5, MADRS-BM, (WHO-QOL)-BREF	Subjects with history of addiction. Prevalence of ED is 67% overall with 26.1% mild ED, 30.4% mild-moderate ED, and 17.2% severe ED. Depression was the only factor found to be associated with ED (OR 3.98 95% CI 1.51–10.40, $P = 0.002$). There is a significant negative association between age and ED score ($r = -0.27$, $P = 0.002$).
Lugoboni et al. 2017 Italy [11]	Cross-sectional	797	MMT(598), BMT (199)	IIEF-2; QHG-12	Subjects with history of addiction. The prevalence of ED was 36.8%. GHQ-12 scores were significantly better in subjects without ED ($P < 0.001$). Daily oral MED was negatively correlated with erectile function: sexually inactive patients with largest amount, followed by patients who report any ED and those without ED with smallest amounts ($P = 0.025$).
Zhao 2017 [16•]	Systematic review and meta-analysis	10 studies	Methadone, opium, heroin, morphine equivalents, opium derivatives	N/A	Pooled results indicated that patients with opioid use had a significantly higher risk of ED than those without opioid use (RR = 1.96, 95% CI = 1.66–2.32, $P < 0.001$). Subgroup analyses showed a stronger association in men younger than 50 years old (RR = 2.21, 95% CI = 1.68–2.91, $P < 0.001$) and men on methadone had a lower risk of ED compared to other types of opioid intervention (RR 1.82, 95% CI 1.15–2.88, $P < 0.05$). There was a significant association between long-term (> 3 years) use of opioid and the risk of ED (RR = 2.25, 95% CI 1.89–2.69, $P < 0.001$). There was a significant association between ED and short term use (4 months to 3 years) (RR 1.97, 95% CI1.34–2.89, $P = 0.001$).

MMT methadone maintenance therapy, *BMT* buprenorphine maintenance therapy, *SD* sexual dysfunction, *ED* erectile dysfunction, *IIEF* International Index of Erectile Dysfunction, *BDI* Beck Depression Inventory, *T* testosterone, *MED* morphine equivalent dose, *TRT* testosterone replacement therapy, *MADRS-BM* Montgomery-Asberg Depression Rating Scale, *WHOQOL-BREF* World Health Organization Quality of Life Scale, *QHG-12* General Health Questionnaire, *N/A* not available

outcome was dosage dependent, particularly for the SA opioids [50]. The same authors subsequently found that men on fentanyl, methadone, and oxycodone are more likely to be androgen deficient compared to men on hydrocodone (OR 25.7, 7.33, and 3.15, respectively) [49]. A possible explanation of these findings is the "nadir hypothesis." Because testosterone in men is produced in a pulsatile fashion periodically throughout every 24-h cycle, the nadirs in drug level that occur more frequently between doses of SA opioids may allow some testosterone to be produced during these nadirs, which may be sufficient to maintain normal testosterone levels. In other words, the pharmacokinetics or formulation of the opioid also plays a role in the degree of hypogonadism in addition to the opioid's direct physiological impact [49].

The relationship between low testosterone level and opioid therapy begs the question of whether men on chronic opioid

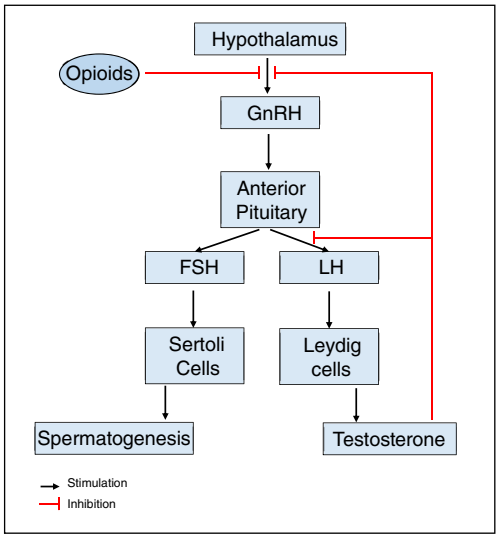

Fig. 1 Opioid effect on the hypo-thalamo-pituitary axis

therapy should be routinely screened for hypogonadism and whether treatment with TRT is beneficial when a diagnosis is made. A prospective study using data from the Testim Registry in the USA showed that hypogonadal men using TRT for 12 months experienced significant changes in total testosterone levels and improvement in sexual function and mood as measured by Brief Male Sexual Function Inventory (BMSFI) and Patient Health Questionaire-9 (PHQ-9) scores, respectively, in both opioid users and nonusers [57]. Similar improvements in sexual function, mood, and body composition were seen in one small open-label pilot study, a small randomized control trial, and a small prospective, pre-post analysis study where TRT was administered to men using opioid therapy for chronic pain [14, 56, 60]. Furthermore, a retrospective pilot study looking at 27 hypogonadal men with chronic non-cancer pain undergoing opioid therapy found that TRT leads to reduced pain levels and decreased opioid requirements [13].

The Endocrine Society recognizes the high prevalence of low testosterone in opioid users and recommends TRT for symptomatic men with classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density [29].

Opioids and Ejaculatory Dysfunction

The International Society for Sexual Medicine (ISSM) defines premature ejaculation (PE) as "ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration from the first sexual experience (lifelong premature ejaculation), a clinically significant and bothersome reduction in latency time, often to about three minutes or less (acquired premature ejaculation) or the inability to delay ejaculation on all or nearly all vaginal penetration with negative personal consequences such as distress, bother, frustration and/or the avoidance of sexual intimacy" [55]. Several studies have reported high prevalence of ejaculatory dysfunction in men taking opioids. However, most of these studies did not focus solely on ejaculatory dysfunction alone [27, 39, 54]. One study with an emphasis on PE found that the prevalence is three times higher in opiate-dependent males than in the general population. Interestingly, the authors also stated that 63.2% of men with lifelong PE reported that heroin helped their PE, whereas 18.4% thought it worsened their PE. In another study looking at men with opioid addiction, 36.8% felt that MMT helped their PE while 26.3% felt that it worsened their PE [52]. There appears to be a positive correlation between chronic opioid therapy and PE. However, the prevalence or causal relationship has not been specifically studied.

Interestingly, tramadol, a synthetic opioid, is recommended as medical therapy for premature ejaculation due to its ability to delay ejaculation [61]. Pooled results from a systematic review and meta-analysis of randomized controlled trials of tramadol for PE suggest that tramadol is significantly more effective than placebo at increasing intra-vaginal ejaculatory latency time (IELT) over eight to 12 weeks compared to behavioral therapy or placebo ($P = 0.0007$) [62]. Another systematic review also supports the use of tramadol as an effective treatment for PE, although the maximum study length was only 18 weeks [53]. Two meta-analyses examining the role of tramadol in PE also concluded that tramadol is effective in improving PE [58, 59]. At this point, further studies are needed to characterize the relationship between the various opioids and PE and the potential benefit of tramadol in opioid-related PE.

Opioids and Male Infertility

Recent literature on opioid-related male infertility is limited. There is evidence suggesting that the human body produces endogenous opioid peptides (EOPs) and their receptors are widely distributed throughout the body including the central nervous system and testes. The effect of EOP and their receptors is to decrease testosterone through inhibition of GnRH release [63]. In a case control study of 142 men with opioid addiction, a significant correlation was demonstrated between opioid use and abnormal semen parameters including decreases in sperm count, concentration, motility, normal morphology, acrosome reaction test, seminal plasma antioxidant status, and DNA fragmentation index. This relationship was dependent on the dosage and duration of opioid use [64].

Table 2 Studies examining the relationship between opioid therapy and hypogonadism

Study	Design	Subjects	Drugs	Scale	Results
Daniell et el. 2002 [42]	Cross-sectional	80	Opioid for back pain (54), controls (26)	Hormone assays	Compared to control subjects, TT, FT, E2, DHT, LH, FSH, and estradiol were much lower in opioid-consuming subjects in a dose-related pattern ($P < 0.0001$). Reported that development of ED since starting opioid therapy was unrelated to opioid dose, FT, or TT. No statistics.
Daniell et al. 2005 [52]	24-Week open-label pilot study	16	men with opioid induced androgen deficiency on TRT	Hormone assays, ADSQ, sexual function (Watts SFQ), mood (PGWB), depression (BDI-II), hematocrit level, BPI-SF	FT and TT were subnormal at baseline which increased to low-normal range on 5 mg/day TRT and to the mid-normal range on 7.5 mg/day TRT (from baseline $P < 0.001$; between TRT doses $P < 0.001$ for FT and $P < 0.01$ for TT). Compared to baseline, men on 7.5 mg/day TRT has significant improvement for: ADSQ score significantly for 7.5 mg/day $P < 0.001$, watts SFQ score for 7.5 mg/day $P < 0.001$, PGWB scores for both 5 and 7.5 mg/day $P < 0.05$, and BDI-II score for 7.5 mg/day $P < 0.001$.
Bliesener et al. 2005 Germany [53]	Cross-sectional	105	MMT (37), BMT (17), controls (51)	SFQ, BDI, hormone assay	Subjects with narcotics addiction. Men on BMT had significantly higher T levels than high-dose MMT (5.1 vs 2.8 ng/mL, $P < 0.0001$). T levels in men on BMT did not differ from healthy controls. Men on BMT had significantly lower frequency of SD compared to MMT subjects ($P < 0.0001$).
Hallinan et al. 2007 [51]	Cross-sectional	103	MMT (84), BMT (19)	Hormone assays	Subjects with history of addiction. 64.5% of men on MMT and 27.8% of men on BMT had TT levels below the laboratory reference range before 13:00 h of receiving opioid. Comparing MMT to age-matched controls ($n = 79$), TT, FT, E2, and LH were significantly lower ($P < 0.0001$). Comparing BMT to age-matched controls ($n = 72$), FT, E2 and LH were significantly lower ($P < 0.01$). Comparing MMT to BMT, TT and FT were significantly lower ($P = 0.001$, $P = 0.01$, respectively).
Aloisi et al. 2011 [54]	Prospective, pre-post analysis	17	men with chronic noncancer pain with morphine induced hypogonadism with 1 year of TRT	Pain assessment: VSA (Visual Analogue Scale), QUID (Italian Pain Questionnaire). Androgen related QOL: AMS (Aging Male's Symptoms). Mood: POMS (profile of Mood State), Epidemiological Studies Depression Scale (CES-D), Level of performance (SF-36); Hormone assays, (place all these acronyms down in the legend)	TT, FT, and bioavailable T were very low at baseline (1.16 ng/mL, 4.33 pg/mL, 0.34 ng/dL, respectively). TT significantly increased by month 3 and remained stable by month 12. FT significantly increased by month 12 ($P < 0.028$). Bioavailable T significantly increased by month 3 ($P < 0.028$) and remained significantly higher at month 12 ($P < 0.018$). Significant improvement in QUID values for various areas of pain ($P < 0.04$); significant improvement in AMS score ($P < 0.03$). Significant improvement in SF-36 Mental Index ($P < 0.04$).
Bawor et al. 2015 [22•]	Systematic review and meta-analysis	17 studies	MMT, BMT, Heroin, unclassified opioid	N/A	Significantly reduced mean T level in men with opioid use compared to controls (mean difference = − 164.78; 95% CI − 245.47, − 84.08; $P < 0.0001$). Methadone did not affect testosterone differently than other opioids.
Blick et al. 2012 [55]	Prospective observational cohort	849	849 hypogonadal men starting on TRT with 90 men using opioids:	Hormone assays, BMSFI questionnaire	Baseline TT and PSA were not statistically different between opioid users and non-users. Both opioid users and non-users had significant increases in TT and FT at 12 months with TRT ($P < 0.001$). Sexual function and mood

Table 2 (continued)

Study	Design	Subjects	Drugs	Scale	Results
			hydrocodone (41), oxycodone (25), morphine (6), buprenorphine (4), codeine (4), propoxyphene (4), oxymorphone (2), tramadol (2), fentanyl (1), methadone (1)		improved significantly in both opioid users and non-users at 12 months of TRT ($P < 0.003$) and significantly correlated with change in TT ($P < 0.001$).
Duarte 2013 [49]	Cross-sectional	20	Men with intrathecal opioid therapy	Hormone assays, DEXA scan for those diagnosed with hypogonadism)	17 (85%) of subjects had hypogonadism (FT < 250 pmol/L). 14 subjects had DEXA scan: 3 subjects with osteoporosis (T score < or = − 2.5 SD) and 7 with osteopenia (T score between − 1.0 and − 2.5 SD). No statistical analysis.
Rubinstein et al. 2014 [56]	Retrospective cohort	1585	men on opioids	Hormone assays	Men on long-acting opioids were more likely to be androgen deficient than men on short-acting opioids (57 vs 35%, $P < 0.001$; OR 3.39; 95% CI 2.39–4.77). Dose was more strongly associated with androgen deficiency in men on short-acting opioids (OR 1.16; 95% CI, 1.09–1.23, for each 10-mg increase in dose) than in men on long-acting opioids (OR 1.01; 95% CI, 1.01–1.02).
Basaria 2015 [14]	Randomized controlled trial, 14 weeks	84	Hypogonadal men on opioids for chronic noncancer pain randomized to TRT (43) and placebo (41)	Brief Pain Inventory (BPI), Quantitative Sensory Testing for pain (QST), IIEF, Medical Outcomes Study Short Form-36, Dual energy X-ray absorptiometry for body composition, hormone assays	TT increased 477 ng/dL ($P < 0.01$) and FT increased 123 pg/mL ($P < 0.01$) in treatment arm compared to placebo. Significant improvement on QST noted for some body areas in treatment arm ($P = 0.03$), no significant improvement in BPI. Treatment arm had increase in sexual desire ($P = 0.05$); this was significantly correlated with T level ($P = 0.002$). Treatment arm had significant reduction in fat mass (0.8 kg, $P = 0.01$).
Rubinstein et al. 2016 [57]	Retrospective cohort	1159	men on opioids	Hormone assays	Compared to men on hydrocodone, ORs for androgen deficiency associated with specific opioid are fentanyl (OR 25.7, 95% CI 2.82–234.97), methadone (OR 7.33, 95% CI 3.29–16.33), and oxycodone (OR 3.15, 95% CI 1.87–5.33). Increase odds for androgen deficiency is seen with increase in dose: hydrocodone (OR 1.18 per 10-mg increase, 95% CI 1.09–1.28) and oxycodone (OR 1.01, 95% CI 1.00–1.02)
Raheem et al. 2017 [13]	Retrospective open pilot	27	Men with hypogonadism on opioids receiving TRT (11) or not receiving TRT (16)	Hormone assay, NPS, ADAM, IIEF	Mean follow-up TT was significantly higher after TRT compared with the non-TST group (497.5 vs 242.4 ng/dL, $P = 0.03$). Median follow-up NPS was 0 and 2 in the TRT and non-TRT groups ($P = 0.02$). Mean MED (mg) decreased by 21 mg in TRT group and increased by 2.5 mg in non-TST group ($P < 0.05$). Median improvement of hypogonadal symptom for ADAM was 3 in TST group compared with 7 in the non-TST ($P < 0.05$). Improvement on IIEF score was not significant.
Ajo et al. 2017 [58]	Cross-sectional	120	Cases (94 opioid dependent	Hormone assays, IIEF	TT, FT, bioavailable T, and salivary T levels were significantly lower in men on opioids with ED ($P < 0.03$).

Table 2 (continued)

Study	Design	Subjects	Drugs	Scale	Results
			men with ED), matched controls (26 opioid dependent men without ED)		
Yee et al. 2018 Malaysia [59]	Cross-sectional	107	MMT (76), BMT (31)	Hormone assay, Mal-IIEF-5, MADRS-BM, OTI	Subjects with history of addiction. 40.8% of men on MMT had TT levels below reference range vs 22.6% men on BMT. Univariate analysis demonstrated that MMT was significantly associated with lower TT than BMT ($P = 0.02$).

TT total testosterone, *FT* free testosterone, *E2* estradiol, *DHT* dihydrotestosterone, *LH* luteinizing hormone, *FSH* follicle stimulating hormone, *ED* erectile dysfunction, *TRT* testosterone replacement therapy, *ADSQ* Androgen deficiency symptoms questionnaire, *SFQ* Sexual Function Questionnaire, *BDI* Beck Depression Index, *BPI-SF* Brief Pain Inventory-short form, *MMT* methadone maintenance therapy, *BMT* buprenorphine maintenance therapy, *T* testosterone, *SD* sexual dysfunction, *IIEF* International Index of Erectile Function, *NPS* Neuropathy Pain Scale, *ADAM* Androgen Deficiency in Aging Male questionnaire, *MED* morphine equivalent dose, *OTI* Opiate Treatment Index, *N/A* not available

Conclusions

Opioids remain the cornerstone of treatment for both acute and chronic pain. Their frequent usage has, however, led to an opioid epidemic with increasing rates of drug-related deaths. Studies clearly demonstrate a higher prevalence of SD in opioid users, specifically ED, hypogonadism, and ejaculatory dysfunction. TRT in patients taking chronic opioids appears to improve SD and decrease the amount of opioids needed to control pain. These findings suggest that routine screening for SD in men on opioid therapy should be considered.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Meldrum ML. The ongoing opioid prescription epidemic: historical context. Am J Public Health. 2016;106(8):1365–6.
2. Gureje O, Von Korff M, Simon G. Persistent pain and wellbeing: a World Health Organization study in primary care. 1998:280: 147–151.
3. Wilkerson RG, Kim HK, Windsor TA, Mareiniss DP. The opioid epidemic in the United States. Emerg Med Clin North Am. 2016;34(2):e1–23.
4. Pathan H, Williams J. Basic opioid pharmacology: an update. Br J Pain. 2012;6(1):11–6.
5. Amoli HA, Golozar A, Keshavarzi S, Tavakoli H, Yaghoobi A. Morphine analgesia in patients with acute appendicitis: a randomised double-blind clinical trial. Emerg Med J. 2008;25(9): 586–9.
6. Davis A. Paracelsus: a quincetennial assessment. J R Soc Med. 1993;86:563–6.
7. Hayes AM, Gilbert SG. Historical milestones and discoveries that shaped the toxicology sciences. In: Molecular, clinical and environmental toxicology. Basel (Switzerland): Birkha¨user Verlag AG. 2009. p. 1–35.
8. Sneader W. The discovery of heroin. Lancet. 1998;352:1697–9.
9. Manchikanti L, SH II, Fellows B, Pampati V, Grider JS. Opioid epidemic in the United States. Pain Physician. 2012;15:ES9–ES38.
10. Rudd RA. Increases in drug and opioid overdose deaths—United States, 2000–2014. 2016:64:1378–1382.
11. Lugoboni F, Zamboni L, Federico A, Tamburin S, for the Gruppo InterSERT di Collaborazione Scientifica (GICS). Erectile dysfunction and quality of life in men receiving methadone or buprenorphine maintenance treatment. A cross-sectional multicentre study. Thumbikat P, editor. PLoS One 2017:12(11): e0188994.
12. Teoh JBF, Yee A, Danaee M, Ng CG, Sulaiman AHB. Erectile dysfunction among patients on methadone maintenance therapy

and its association with quality of life. J Addict Med. 2017;11(1): 40–6.
13. Raheem OA, Patel SH, Sisul D, Furnish TJ, Hsieh T-C. The role of testosterone supplemental therapy in opioid-induced hypogonadism: a retrospective pilot analysis. Am J Mens Health. 2017 Jul;11(4):1208–13.
14. Basaria S, Travison TG, Alford D, Knapp P, Teeter K, Cahalan C, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. Pain. 2015;156(2):280–8.
15.• Yee A, Loh HS, Hisham Hashim HM b, Ng CG. The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study. J Sex Med. 2014;11(1):22–32. T**his meta-analysis consolidated multiple studies and provided statistical result to demonstrate a significantly higher risk of ED in men on methadone compared to buprenorphine therapy.**
16.• Zhao S, Deng T, Luo L, Wang J, Li E, Liu L, et al. Association between opioid use and risk of erectile dysfunction: a systematic review and meta-analysis. J Sex Med. 2017;14(10):1209–19. **This meta-analysis included ten studies, many of which were included in our review, and provided statistical result demonstrating an increased risk of ED associated with opioid use.**
17. Quaglio G, Lugoboni F, Pattaro C, Melara B, Mezzelani P, Des Jarlais DC. Erectile dysfunction in male heroin users, receiving methadone and buprenorphine maintenance treatment. Drug Alcohol Depend. 2008;94(1–3):12–8.
18. Venkatesh K, Mattoo SK, Grover S. Sexual dysfunction in men seeking treatment for opioid dependence: a study from India. J Sex Med. 2014;11(8):2055–64.
19. Kumsar NA, Kumsar ş, Dilbaz N. Sexual dysfunction in men diagnosed as substance use disorder. Andrologia. 2016;48(10):1229–35.
20. Aggarwal N, Kherada S, Gocher S, Sohu M. A study of assessment of sexual dysfunction in male subjects with opioid dependence. Asian J Psychiatry. 2016;23:17–23.
21. Ramdurg S, Ambekar A, Lal R. Sexual dysfunction among male patients receiving buprenorphine and naltrexone maintenance therapy for opioid dependence. J Sex Med. 2012;9(12):3198–204.
22.• Bawor M, Bami H, Dennis BB, Plater C, Worster A, Varenbut M, et al. Testosterone suppression in opioid users: a systematic review and meta-analysis. Drug Alcohol Depend. 2015;1–9:149. **This meta-analysis provides evidence to support the statistical correlation between opioid use and low testosterone.**
23. Hallinan R, Byrne A, Agho K, McMahon C, Tynan P, Attia J. Erectile dysfunction in men receiving methadone and buprenorphine maintenance treatment. J Sex Med. 2008;5(3): 684–92.
24. Deyo RA, Smith DHM, Johnson ES, Tillotson CJ, Donovan M, Yang X, et al. Prescription opioids for back pain and use of medications for erectile dysfunction. Spine. 2013;38(11):909–15.
25. Johannes CB, Araujo AB, Feldman HA, Derby CA, Kleinman KP, McKinlay JB. Incidence of erectile dysfunction in men 40-69 years old: longitudinal results from the Massachusetts Male Aging Study. J Urol. 2000;163(2):460–3.
26. Bacon CG, Mittleman MA, Kawachi I, Giovannucci E, Glasser DB, Rimm EB. Sexual function in men older than 50 years of age: results from the health professionals follow-up study. Ann Intern Med. 2003;139(3):161–8.
27. Bang-Ping J. Sexual dysfunction in men who abuse illicit drugs: a preliminary report. J Sex Med. 2009;6(4):1072–80.
28. Brown R, Balousek S, Mundt M, Fleming M. Methadone maintenance and male sexual dysfunction. J Addict Dis. 2005;24(2):91–106.
29. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59.
30. Cioe PA, Friedmann PD, Stein MD. Erectile dysfunction in opioid users: lack of association with serum testosterone. J Addict Dis. 2010;29(4):455–60.
31. Chen W, Li X, Li X, Ling L, Xia Y, Chen J, et al. Erectile dysfunction among male heroin addicts receiving methadone maintenance treatment in Guangdong, China. J Addict Med. 2012;6(23):212–8.
32. Duarte RV, Raphael JH, Southall JL, Labib MH, Whallett AJ, Ashford RL. Hypogonadism and low bone mineral density in patients on long-term intrathecal opioid delivery therapy. BMJ Open. 2013;3(6):e002856.
33. Nik Jaafar NR, Mislan N, Abdul Aziz S, Baharudin A, Ibrahim N, Midin M, et al. Risk factors of erectile dysfunction in patients receiving methadone maintenance therapy. J Sex Med. 2013;10(8): 2069–76.
34. Zhang M, Zhang H, Shi CX, McGoogan JM, Zhang B, Zhao L, et al. Sexual dysfunction improved in heroin-dependent men after methadone maintenance treatment in Tianjin, China. Chang AYW, editor PLoS One 2014:9(2):e88289.
35. Somani B, Khan S, Donat R. Screening for metabolic syndrome and testosterone deficiency in patients with erectile dysfunction: results from the first UK prospective study: Screening metabolic syndrome and testosterone and testosterone deficiency in men with ED. BJU Int. 2010;106(5):688–90.
36. Babakhanian M, Haghdoost AA, Afshari M, Taghizadeh F, Moosazadeh M. Methadone replacement therapy and sexual disorders among opium dependent Iranian men: a meta-analysis health 2017: 9(1):10.
37. Payte JT. A brief history of methadone in the treatment of opioid dependence: a personal perspective. J Psychoactive Drugs. 1991;23(2):103–7.
38. Teusch L, Scherbaum N, Böhme H, Bender S, Eschmann-Mehl G, Gastpar M. Different patterns of sexual dysfunctions associated with psychiatric disorders and psychopharmacological treatment. Pharmacopsychiatry. 1995;28(3):84–92.
39. Yee A, Loh HS, Hisham Hashim HMB, Ng CG. Clinical factors associated with sexual dysfunction among men in methadone maintenance treatment and buprenorphine maintenance treatment: a meta-analysis study. Int J Impot Res. 2014;26(5):161–6.
40. Yee A, Danaee M, Loh HS, Sulaiman AH, Ng CG. Sexual dysfunction in heroin dependents: a comparison between methadone and buprenorphine maintenance treatment. Dominguez JM, editor PloS One 2016:11(1):e0147852.
41. Spring WD, Willenbring ML, Maddux TL. Sexual dysfunction and psychological distress in methadone maintenance. Int J Addict. 1992;27(11):1325–34.
42. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain. 2002;3(5):377–84.
43. Wong D, Gray D, Simmonds M, Rashiq S, Sobolev I, Morrish DW. Opioid analgesics suppress male gonadal function, but opioid use in men and women does not correlate with symptoms of sexual dysfunction. Pain Res Manag. 2011;16(5):311–6.
44. Araujo AB, O'Donnell AB, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2004;89(12):5920–6.
45. Köhler TS, Kim J, Feia K, Bodie J, Johnson N, Makhlouf A, et al. Prevalence of androgen deficiency in men with erectile dysfunction. Urology. 2008;71(4):693–7.
46. Kupelian V, Shabsigh R, Travison TG, Page ST, Araujo AB, McKinlay JB. Is there a relationship between sex hormones and erectile dysfunction? Results from the Massachusetts Male Aging Study. J Urol. 2006;176(6):2584–8.

47. Talha M, Bilal G, Gökhan T, Arı Z, Coşkun B. A relationship of sex hormone levels and erectile dysfunction: which tests should be done routinely? Yonsei Med J. 2007;48(6):1015–9.
48. Hallinan R, Byrne A, Agho K, McMahon CG, Tynan P, Attia J. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. Int J Androl. 2009;32(2):131–9.
49. Rubinstein AL, Carpenter DM. Association between commonly prescribed opioids and androgen deficiency in men: a retrospective cohort analysis. Pain Med. 2016:pnw182.
50. Rubinstein A, Carpenter DM. Elucidating risk factors for androgen deficiency associated with daily opioid use. Am J Med. 2014;127(12):1195–201.
51. Katz N, Mazer NA. The impact of opioids on the endocrine system. Clin J Pain. 2009;25(2):170–5.
52. Chekuri V, Gerber D, Brodie A, Krishnadas R. Premature ejaculation and other sexual dysfunctions in opiate dependent men receiving methadone substitution treatment. Addict Behav. 2012;37(1):124–6.
53. Wong BLK, Malde S. The use of tramadol "on-demand" for premature ejaculation: a systematic review. Urology. 2013;81(1):98–103.
54. Grover S, Mattoo S, Pendharkar S, Kandappan V. Sexual dysfunction in patients with alcohol and opioid dependence. Indian J Psychol Med 2014:15:36(4):355–65.
55. Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the Second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. Sex Med. 2014;2(2):41–59.
56. Aloisi A, Ceccarelli I, Carlucci M, Suman A, Sindaco G, Mameli S, et al. Hormone replacement therapy in morphine-induced hypogonadic male chronic pain patients. Reprod Biol Endocrinol. 2011;9(1):26.
57. Blick G, Khera M, Bhattacharya RK, Nguyen D, Kushner H, Miner MM. Testosterone replacement therapy outcomes among opioid users: the Testim Registry in the United States (TRiUS). Pain Med. 2012;13(5):688–98.
58. Wu T, Yue X, Duan Y, Luo D, Cheng Y, Tian Y, et al. Efficacy and safety of tramadol for premature ejaculation: a systematic review and meta-analysis. Urology. 2012;80(3):618–24.
59. Yang L, Qian S, Liu H, Liu L, Pu C, Han P, et al. Role of tramadol in premature ejaculation: a systematic review and meta-analysis. Urol Int. 2013;91(2):197–205.
60. Daniell HW, Lentz R, Mazer NA. Open-label pilot study of testosterone patch therapy in men with opioid-induced androgen deficiency. J Pain. 2006;7(3):200–10.
61. Althof SE, McMahon CG. Contemporary management of disorders of male orgasm and ejaculation. Urology. 2016;93:9–21.
62. Martyn-St James M, Cooper K, Kaltenthaler E, Dickinson K, Cantrell A, Wylie K, et al. Tramadol for premature ejaculation: a systematic review and meta-analysis. BMC Urol. 2015;15:6.
63. Subirán N, Casis L, Irazusta J. Regulation of male fertility by the opioid system. Mol Med. 2011;12(7–8):846–53.
64. Safarinejad MR, Asgari SA, Farshi A, Ghaedi G, Kolahi AA, Iravani S, et al. The effects of opiate consumption on serum reproductive hormone levels, sperm parameters, seminal plasma antioxidant capacity and sperm DNA integrity. Reprod Toxicol. 2013;36:18–23.