



## Association Between Opioid Use and Risk of Sexual Dysfunction: A Systematic Review

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### ABSTRACT

Opioid use disorder (OUD) is defined by negative effects on oneself despite numerous efforts to stop it. Chronic opioid users have sexual dysfunctions such as erectile dysfunction, delayed ejaculation decreased libido, and sexual performance. To explore the association between the use of opioids and the risk of sexual dysfunction. This review was conducted from March 2023 to June 2023, and comprised of search on PsycINFO, MEDLINE, EMBASE, Google Scholar, OvidSP Science Direct, PubMed, Clinical Trials.gov, and Web of Science databases for experimental studies and randomized controlled trials related to OUDs published in peer-reviewed English-language journals between 2013 and 2023 (10 years). Of the 314 studies initially identified, 41(13%) were subjected to full-text assessment, and 10 were reviewed and analysed (Figure). There were 2(20%) each study done in Egypt and Istanbul and 1(10) each in Germany, Canada, Spain, China, Poland, and Malaysia. All 10 (100%) studies were based on opioid use and sexual dysfunction. Prospective studies showed that the occurrence of any sexual dysfunction ranged from 40% to 90% of opioid dependence. The most commonly studied observed sexual dysfunction is a lack of desire, erectile dysfunction, erectile dysfunction, and poor satisfaction. Our findings suggest that there is a significant link between opioid use and sexual dysfunction and that people who use opioids have higher rates of sexual dysfunction. Nevertheless, opioids have mind-altering properties that negatively affect various stages of the sexual cycle.

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## 1. Introduction

Opioid use disorder (OUD) is a common mental health issue that causes mortality and morbidity (Morin et al., 2020). "Opioids" refers to a class of drugs that includes alkaloid compounds derived directly from the resin of opium poppy (heroin and morphine) and synthetic compounds (hydromorphone and oxycodone) (Zedler et al., 2014). Opioids are responsible for the majority of prescription drug abuse (Singhal et al., 2016). Inability to control the use of opioids, despite efforts to cut down and ongoing tolerating, and withdrawal issues are the most common signs and symptoms. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5-TR) defines OUD as a problematic pattern of use that leads to distress with at least two or more eleven problems within 12 months (Taylor & Samet, 2022). Globally, Opioid abuse, including heroin, morphine, and prescription pain relievers, is a thoughtful issue that affects every aspect such as the economic, social, well-being, and health of all societies (Salmond & Allread, 2019). According to one survey, it is predictable that 36 million people worldwide abuse opioids (Dargan & Wood, 2012). Another report, in 2019 showed that 9.5 million American individuals misused opioids in the previous year. In the same way, another study reported that OUD affected 1.5 million American individuals in the last year (Reif et al., 2021). In Pakistan,

the consumption of opiates such as heroin and non-medical use of prescription opioid painkillers like oxycodone has reached epidemic levels, and rates are still rising (Porucznik et al., 2010). According to estimates, 320,000 people (0.3 percent) and 860,000 people (0.8 percent) regularly use opium and heroin. 1.06 million individuals total (1.0 percent, aged 15-64 years) are using opiates (Survey\_Report\_Final\_2013.pdf.).

Opioids, a class of medications widely used for pain management, have garnered significant attention for their potential impact on sexuality (Kerrigan & Goldberger, 2020). Opioids are involved in sexual function. Sexuality is a necessary part of life. Sexual dysfunction is a clinically significant negative consequence of opioid and heroin addiction. In females, numerous sexual issues are noticed such as amenorrhea and reduced fertility and libido have been observed in chronic opioid addicts. Sexual dysfunction (SD) is defined as the "incapacity to complete sexual intercourse because of decreased sexual desire, arousal, or orgasm (Daniell, 2008). SD has been linked to psychological issues such as depression, fatigue, and decreased mobility in some studies. Opiates can cause sexual disorders such as erectile dysfunction by shifting blood circulation away from the genital organs and toward other organs. Opiates can suppress testosterone production (Bawor et al., 2014).

According to a study, It was demonstrated that synthetic opioid dependency had not only effect an effect on sexual functions but also on men's level of sexual esteem, in which they experience low sexual preoccupation (El-Sheikh, Abolmagd, Abdelazim, & Enaba, 2017). However, in addition to their analgesic properties, opioids have garnered significant attention for their potential impact on sexuality and the complex relationship between these substances and sexual dysfunction (Ghadigaonkar & Murthy, 2019; Macintyre & Schug, 2021). Understanding the effects of opioids on sexuality is essential for informing clinical practice, guiding patient care, and addressing the complex relationship between opioid use and sexual function. The effects of opioids on sexual desire have been a subject of investigation in recent years. Studies have revealed that opioids, by interacting with the brain's reward circuitry and neurotransmitter systems, can impact sexual desire and behavior and develop sexual dysfunction (Browne, Godino, Sallery, & Nestler, 2020).

The relationship between the use of opioids and sexual dysfunction is not universally straightforward. While some individuals may experience an increase in sexual desire while using opioids, others may report no change or even a decrease (Austin & Short, 2020; Birke, Ekholm, Højsted, Sjøgren, & Kurita, 2019). These variations in response highlight the importance of individual factors and underscore the complexity of the interaction between opioids and sexuality. This systematic review provides an opportunity to comprehensively examine the existing literature on this topic, synthesizing the available evidence to enhance our consideration of the intricate interchange between opioids, sexuality, and dysfunction. The ethical considerations surrounding the use of opioids for decreasing sexual desire are complex and multifaceted. While opioids have legitimate medical applications in pain management, using them solely to manipulate sexual desire raises important ethical questions. Concerns include the potential risks and consequences associated with prolonged opioid use, such as the development of addiction, dependency, and other adverse effects on mental and physical health. Balancing the potential aids of opioid use and hazards in the framework of sexuality requires careful evaluation, individualized consideration, and an understanding of the broader implications.

To date, the available literature on the direct influence of opioids on sexuality remains limited and fragmented. Existing studies primarily consist of case reports, retrospective analyses, and indirect observations, lacking a comprehensive overview of the topic. A systematic review study aims to report this gap in knowledge by conducting a comprehensive and review search of the literature, selecting relevant studies, and synthesizing their findings. By critically evaluating the existing evidence, a systematic review can provide a comprehensive overview of the effects of opioids on sexual dysfunction, identify gaps in knowledge, and offer recommendations for future research and clinical practice (Jones et al., 2020). By conducting a systematic review of the connotation between opioid use and the risk of sexual dysfunction. The findings of this review will provide evidence-based insights for healthcare professionals, researchers, and individuals facing decisions related to opioid use and its impact on sexuality. Additionally, a systematic review can serve as a valuable resource to guide clinical practice, inform patient counseling, and

foster further research to address the multifaceted interplay between opioid use and the risk of sexual dysfunction.

## **1.2. Significance of Study**

One of the negative consequences of OUD is sexual dysfunction, which can have a major effect on the patient's quality of life. For healthcare providers to make educated treatment decisions, manage patients' expectations, develop comprehensive interventions, and improve the well-being of this population, we need to better understand the connections between OUD and sexual dysfunction. In addition, the study compares OUD patients who have experienced sexual dysfunction in the past to those who have not. This study will aid in the creation of targeted interventions that address the unique challenges faced by people with OUD by identifying the specific factors that contribute to sexual dysfunction. In conclusion, a systematic review of the relationship between opioid use and the risk of sexual dysfunction is important because of the knowledge it can provide clinicians, patients, researchers, and public health advocates in their fight against the ill effects of opioid abuse.

## **2. Method and Material**

This review focused on empirical studies published in the last ten years, with no weight on studies that were published before 2013.

### **2.1. Search Strategy**

This review study thoroughly searches for related literature in databases such as Science Direct, PsycINFO, Scopus, Google Scholar, MEDLINE, Web of Science, PubMed, and OvidSP from 2013 to 2023 (10 years). The examination was only restricted to studies that were based on the English language involving human adolescents as participants. From March 2023 to June 2023, a new search was conducted.

### **2.2. Search Terms**

The keywords or search terms were: 1) "substance abuse of opioid\*" OR "opioid\*" OR "OUD\*" OR "Heroin\*" OR "opium\*" OR "addiction Opioid opiate\*" OR "Oxycodone\*" OR "Opioid use disorder\*". AND 2) "Sexual dysfunction\*" OR "sexual performance\*" OR "erectile dysfunction\*" OR "delayed ejaculation\*".

### **2.3. Steps in Systematic Review Process**

The following procedures were used in this systematic review:

- Look into existing reviews.
- Determine the review question,
- Create criteria for inclusion and exclusion.
- Look for research
- Choose research for inclusion-based criteria.
- Compile data
- Assess the risk of bias from studies.
- Results and evaluate evidence quality

### **2.4. Inclusion and Exclusion Criteria**

The present review only comprised of studies that met the mentioned below criteria:

- English-language articles;
- studies examining opioid use and sexual dysfunction.
- Both (qualitative and quantitative) studies were considered.

These researches, on the other hand, were excluded if;

- Not have complete access to studies.
- Not in English
- Non-humans, gays, or lesbians were not included.

## **2.5. Selection Process**

Initially, the references were found during the search and imported into EndNote and then into Excel. The articles were evaluated for suitability based on the criteria (inclusion and exclusion) after the titles and abstracts were screened. Figure 1 depicts the selection procedure.

## **2.6. Data Extraction**

From each study, the following details were extracted:

Participants' age, Gender, sample size/description, study country, parenting assessment, study type/design, use of opioids, and sexual dysfunction.

The researcher coded the three classes of opioids alkaloids, semi-synthetic, and synthetic. These types and other articles extracted were considered. The studies that used opioids were included, while the articles that used other substances such as stimulants, depressants, and hallucinogens were excluded. In this review, the research was solely focused on examining the association between the use of opioids and the risk of sexual dysfunction.

The review included experimental studies and randomized controlled trials (RCTs) related to OUDs in adolescents and adults published in peer-reviewed English-language journals. The studies, either qualitative or quantitative, provided data relating to individuals suffering from OUDs according to DSM-5-TR.

## **2.7. Quality Assessment**

A list was used to measure the research's quality and to recognize threats to validity (internal and external). Each study was evaluated using specific criteria, which included descriptive basis, population, data collection, generalizability, study completion, analysis, and interpretation.

## **2.8. Information Analysis**

In this review, studies on opioid use, psychological difficulties, and sexual dysfunction were restricted to non-clinical samples. Separately, the results of each study were examined and classified on the relation between constructs, such as opioids and sexual dysfunction.

## **3. Result**

Of the 314 studies initially identified, 41(13%) were subjected to full-text assessment, and 10 were reviewed and analysed (Figure). There were 2(20%) each study done in Egypt and Istanbul and 1(10) each in Germany, Canada, Spain, China, Poland, and Malaysia. All 10 (100%) studies were based on opioid use and sexual dysfunction. There were 5 (50%) studies using Cross-sectional design that showed significant results that dose and duration of opioid use are related to evidence of sexual dysfunction rest studies used different research designs that reported significant results simultaneously while addressing multiple patient variables (Tables 1-2). A variety of instruments were used to assess opioid use and sexual dysfunction. Prospective studies found that sexual dysfunction was common in opioid use disorders. In studies, the occurrence of sexual dysfunction ranged from 40% to 90% of opioid dependence. Sexual dysfunctions of various types were recognized, including lack of desire, poor satisfaction, premature ejaculation, and erectile dysfunction. The most common study of sexual dysfunction was erectile dysfunction. Sexual dysfunctions were consistently associated with comorbidity and socioeconomic deprivation.

Two (12.5%) of the studies examined the levels of sex hormones in opioid-dependent patients. These studies compare the sexuality and sex hormone levels of opioid-dependent males to non-substance-dependent males (Abdelazim et al., 2015; El-Sheikh et al., 2017). These studies revealed that opioid dependency had not only an effect on the sexual functions of dependent men but also their level of sexual esteem also affected.

Furthermore, 2(12.5%) studies analyzed that Prescription Opioids also become a risk for Erectile dysfunction (Ajo et al., 2017). Before the prescription, the patients who reported sexual dysfunction, the intensity of the pain, erectile function, quality of sexual life, and testosterone levels were all assessed. After a 6-month follow-up, the researchers discovered that the dose and duration of opioids were connected to erectile dysfunction. This result could help make

decisions for long-term opioid use. Furthermore, 1(6.25%) study (Ağaçhanlı, Alniak, & Evren, 2018) provides data on sexuality and related factors among women with OUD. The study involved 51 outpatient women with OUD who were on Buprenorphine/Naloxone opioid maintenance treatment (OMT) (Incoronato, Biedermann, Roth, Müller, & Fuss, 2023).

A randomized controlled study found that naltrexone (Opioid) has a significant negative effect on sexual arousal. The participants (N = 64, n = 32 women) were requested to the laboratory twice at a four-week interval. During the study, physiological functions such as disgust sensitivity, sexual arousal, and pain perception, during the sexual response cycle (SRC) is determined. Another cross-sectional study found that male opiate addicts have a lower mean score for sexual desire ( $p=0.001$ ) (Yee et al., 2019). According to the findings, the prevalence of sexual dysfunction ranged between 21 and 52%. Another study (Ajo et al., 2017). (Ajo et al., 2017) found that over the course of three years of follow-up, the prevalence of sexual dysfunction (SD) was 33% of cases that reported reduced libido and/or ED. ED was confirmed in 27.6% of these (105/380 patients).

In another Cross-sectional design study (Bawor et al., 2014), Opiate (narcotic) analgesics such as methadone are in a class of medications. Between June and December of 2011, this study 231 patients with opioid addiction from methadone clinics were recruited. All demographic information such as substance use, psychiatric history, urine, and blood samples were collected after enrollment while the control group comprised 783 non-opioid-using adults. The result shows that methadone had significantly lower testosterone levels than controls. Whereas methadone had no effect on testosterone levels among women.

Among methadone patients, it was concluded that testosterone level was significantly linked with dose in men only. Similarly, another study (2021) discovered that long-term opioid use for chronic pain is linked to sex hormone disruptions. According to the finding, disturbances in sex hormones and sexual function were investigated. According to the findings, 50% reduction in pain intensity and daily function interfering over the previous week by following opioid treatment, and 60% of men and women reported decreased sexual desire and function (Ho et al, 2021).

#### **4. Discussion**

To our data, no study examines the relationship between opioid use and the risk of sexual dysfunction (SD). Because opioids are commonly used and their impact on libido and quality of sexual function is critical. This review determines to create current knowledge on the relationship between opioid use and the occurrence of sexual dysfunctions. Numerous studies show that opioid use harms sexual life and becomes the reason for sexual dysfunction in both men and women. All ten (100%) studies on opioid use and sexual dysfunction concluded that SD is of high clinical relevance. Hence, it is frequently overlooked and unexplored in routine clinical care. According to this review, long-term opioid use is connected with sexual dysfunctions and includes decreased libido and sexual performance, erectile dysfunction, and delayed ejaculation. This finding is constant with existing studies that chronic opioid dependency is strongly linked to sexual dysfunctions in men, for instance, diminished libido, erectile dysfunction, and delayed ejaculation (Butler, Budman, Fanciullo, & Jamison, 2010).

Similarly, Cushman and Kreek also discovered a negative association between high-dose methadone and low levels of plasma testosterone. Other descriptions for opioid-induced sexual dysfunction contain the activation of alpha-adrenergic blocking of opioids, which straight influences the function of sex organs, and psychological factors, for example, drowsiness, euphoria, and untidy lifestyle (Al-Gommer, George, Haque, Moselhy, & Saravanappa, 2007). Additionally, SD rates in patient roles with heroin dependence, MMT, or BMT are higher than in the general public, with rates ranging from 34-85% for heroin dependency, such as 14-81% for MMT, 36-83% for BMT, and 90% for naltrexone maintenance (Grover et al., 2014). In terms of sexuality, the study's findings are consistent with anecdotal reports indicating a high occurrence of sexual problems in opiate user people. Sexual dysfunction in men associated with opiate use has been linked to a decrease in gonadotropin-releasing hormone and LH, resulting in lower plasma testosterone levels (El-Sheikh et al., 2017). Opioids of all types, including heroin and methadone have been originating to deteriorate these conditions. Before substance abuse, a substance-using population had a high occurrence of erectile dysfunction (20.3%) and premature ejaculation (37.5%).

It was hypothesized that sexual problems are a risk factor for opioid misuse in men (Ormston et al., 2023). In contrast to men, women are also affected by opioid use. Even without OUD, among women, sexual functioning is a complex process. It can be influenced by numerous factors such as biological, medical, psychological, sociocultural, economic, and interpersonal (Goetz, Becker, & Mazure, 2021). In addition to important physiological and pharmacological components, the association between the use of opioids and sexuality includes psychological, social, and cultural mechanisms (Kosten & George, 2002).

The current systematic review concluded that sexual life is also affected by the use of opioids among men and women. The common sexual issues in men are a lack of sexual desire and erectile dysfunction (ED) (Sadovsky et al., 2010) while among women are vaginal dryness and other genital changes that source of pain during sexual activity, or loss of sexual desire, which is often accompanied by difficulty feeling arousal and pleasure during sex (Finch, Evans, & Narod, 2012). Sexual dysfunction is more predominant among women compared to men. Similarly, the research also shows that opioids affect the endocrine system (both endogenous and exogenous) and show a significant role in sexual functioning. Because of this, they are less likely to touch and adore being touched than the control group.

Furthermore, when compared to another group, vaginal penetration, and orgasm functions were diminished (Brennan, 2022). Similarly, it was also discovered that women with OUD had higher rates of SD and they were less likely to involve in sexual intercourse and preferred to discuss sexuality less with their buddies which eventually affect their sexual relationships (Yee et al., 2019). In our study, we looked at how SD symptoms changed in men with chronic pain who were receiving long-term opioid therapy. SD was found to be very common, with a prevalence of 27.3%, which was consistent with the medical literature (Kerrigan & Goldberger, 2020). This finding is also consistent in developing countries, indicating a relatively high occurrence of erectile dysfunction among males. According to a more recent general population study from India, sexual dysfunction affects 14% of women and 21.2% of men (Rao, Darshan, & Tandon, 2015).

However, this review concluded that initial opioid use causes delayed ejaculation in men and perfection in vaginismus in women, resulting in the observation of better-quality sexual function. Opioid use, for instance, morphine and heroin, diminishes the release of luteinizing hormone, resulting in lower testosterone and estradiol levels with an increase in free sex hormone binding globulin, resulting in hypogonadism (Vuong, Van Uum, O'Dell, Lutfy, & Friedman, 2010). As a result, this finding is linked to decreased sexual yearning, erectile dysfunction, and infertility. Chronic opioid use is also linked to lower adrenal androgen production (dehydroepiandrosterone—DHEA, dehydroepiandrosterone sulfate—DHEAS, and androstenedione) (Ghadigaonkar & Murthy, 2019). Long-term opioid substitution therapy has similar effects on sexual function, though methadone is used more than buprenorphine (Rao et al., 2015).

## **5. Conclusion**

Our findings suggest that there is a strong connection between the use of opioids and sexual dysfunction and that people who use opioids have higher rates of sexual dysfunction. Although opioids are thought to be a major cause of nerve, blood vessel, and hormone damage that underpins normal sexual function. However, all opioids used for their mind-altering properties have a variety of negative effects on various stages of the sexual cycle. Awareness of sexual dysfunction is a vital preventive approach for reducing opioid use.

### **5.1 Limitations and Suggestions for Future Research**

Several limitations need to be addressed. 1. The researchers used self-rating rulers to evaluate SDs, and self-reporting may have resulted in biased interpretation due to personal preferences. 2. Most research on the sexual functioning of people with OUDs is conducted on men. We know very little about sexuality and connected features in women suffering from OUD. 3. Patients with OUDs were taking antidepressants and psychostimulants, which may have influenced sexual function parameters. 4. Another limitation is that the stressor variables (duration and severity of the abuse), which can harm sexual behaviors, were not considered.

Future studies ought to build on comparisons made by analyzing the relationship between various opioids and erectile dysfunction. Opioid comparisons between different classes or between short- and long-acting opioids may yield useful information.

Second, work on creating or improving validated measurement tools for identifying sexual dysfunction in people who use opioids. The specific nuances of sexual dysfunction caused by opioid use may not be captured by existing tools. Women, the elderly, and people living with chronic pain should be given more consideration in future research. More research is needed to determine if these communities have any distinctive features or vulnerabilities.

## 5.2. Study Implications

Implications for practice from this systematic review include the need to pinpoint specific risk factors for sexual dysfunction in opioid users, such as dosage, duration of use, specific opioids used, and patient characteristics linked to opioid use. On the other hand, these findings can educate healthcare providers like doctors and pharmacists about the potential sexual risks of opioid use.

Secondly, patients who have been prescribed opioids can benefit from the review's findings, which can be used to inform educational materials and interventions. Patients will be better able to make educated decisions about their treatment and access necessary support and interventions if they are made aware of the potential sexual side effects. Finally, this analysis may help us better understand the effects of various treatment approaches for opioid-induced sexual dysfunction. This information can help doctors decide between different pain relief options or fine-tune their patients' opioid dosages to reduce unwanted sexual side effects.

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## Appendix A

Title	Study Reference	Country	Study Type/Design	Sample Characteristics
The influence of opioid blockage on the sexual response cycle: A randomized placebo-controlled experiment with relevance for the treatment of Compulsive Sexual Behavior Disorder (CSBD)	(Deyo et al., 2013) (Incoronato et al., 2023)	German	double-blind, placebo-controlled, cross-over design	N=64
Gender Differences in Depression and Sex Hormones among Patients Receiving Long-Term Opioid Treatment for Chronic Noncancer Pain in Taiwan—A Multicenter Cross-Sectional Study	(Ho et al., 2021)	Taiwan	cross-sectional multicenter survey	N=100
Sexual Adverse Effects and Erectile Dysfunction During Buprenorphine/Naloxone Combination Treatment for Opioid Use Disorder	(Bestepe, Tunali, & Saridoğan, 2020)	Istanbul	Cross-sectional descriptive study	N=135
A comparison of sexual desire in opiate-dependent men receiving methadone and buprenorphine maintenance treatment	(Yee et al., 2019)	Malaya	Cross-sectional study	N=126
Sexual Dysfunctions are Predicted by Childhood Sexual Abuse in Women with Opioid Use Disorder	(Ağaçhanlı et al., 2018)	Istanbul	Case Control Study	N=99
Erectile dysfunction in patients with chronic pain treated with opioids	(Ajo et al., 2017)	Spain	Prospective observational study	N=105
The assessment of sexuality and sex hormone levels in a group of synthetic opioid-dependent patients	(El-Sheikh et al., 2017)	Egypt	Case-control study	N=60
Sexual Dysfunction and sex hormone levels in Egyptian opioid- Dependent Males	(Abdelazim et al., 2015)	Egypt	Prospective case-control study	N = 60
Methadone-induced testosterone suppression in patients with opioid addiction	(Bawor et al., 2014)	Ontario, Canada.	Cross-sectional design	N=231
Prescription Opioids for Back Pain and Use of Medications for Erectile Dysfunction	(Deyo et al., 2013)	USA	Cross-sectional analysis	N=11327

Note: RCT: Randomized controlled trials

## Appendix B: Assessment of Variables N= 10

Sr. No	Construct	Conclusion
1	Multi-6 Drogentest	Naltrexone negatively affects sexual arousal and its impact on prolactin levels may explain its efficacy in treating CSBD.
2	MME	Prolonged opioid therapy for chronic noncancer pain is associated with low sex hormone levels, reduced sexual function, and higher risks of depression, particularly in women.
3	GRISS, IIEF-5	Bup/Nal treatment group exhibited more severe erectile dysfunction (ED) and communication issues compared to the control group, while overall sexual dysfunction scores did not differ significantly.
4	SDI-2, Mal-IIEF-15, MADRS-BM	Patients on methadone maintenance therapy (MMT) exhibited lower sexual desire, lower dyadic sexual desire, and lower total testosterone levels compared to patients on buprenorphine maintenance therapy (BMT)
5	GRISS, CTQ-28, BDI	Childhood sexual abuse in women with opioid use disorder (OUD) predicts sexual dysfunctions, along with higher levels of depression and anxiety.

	STAI	
6	VAS, IIEF-EF, EQ-VAS, AND MSLQ-QOL, HAD	Andrological treatment improved sexual function, quality of life, and anxiety in chronic opioid users, emphasizing the importance of addressing sexual health in pain management.
7	Sexuality scale ILEF and sex hormone levels.	Synthetic opioid dependency negatively affects sexual function and hormone levels in men, leading to decreased sexual esteem, increased sexual depression, and altered levels of testosterone and prolactin.
8	The Sexuality Scale and ILEF	The study concludes that opioid-dependent male inpatients exhibit sexual dysfunctions and hormonal imbalances, with higher luteinizing hormone levels associated with more severe sexual depression.
9	Serum total testosterone level	Men undergoing methadone treatment had significantly lower testosterone levels, while testosterone levels in women on methadone treatment did not differ significantly.
10	The characterization of opioid use among ambulatory adult males with back pain	Long-term opioid use and higher doses were linked to increased use of medications for erectile dysfunction or testosterone replacement.

Note: ILEF: International Index of Erectile Function, ASI: The Addiction Severity Index, VAS: Visual analog scale, IIEF-EF: International Index Of Erectile Function- Erectile Function Domain, EQ-VAS: EuroQoL Visual Analog Scale, MSLQ-QOL: Male Sexual Life Quality Questionnaire, HAD: Hospital Anxiety and Depression Scale, GRISS: Golombok-Rust Inventory of Sexual Satisfaction, CTQ-28: Childhood Trauma Questionnaire, BDI: Beck Depression Inventory, STAI: The State-Trait Anxiety Inventory (STAI), SDI-2:Sexual Desire Inventory, Mal-IIEF-15: The Malay version of the International Index of Erectile Function, MADRS-BM: the Malay version of the Montgomery- Asberg Depression Rating Scale, IIEF-5:International Index of Erectile Function-5, MME: Opioid prescription verification daily oral morphine milligram equivalent, FSFI: the Female Sexual Function Index, IIEF: the International Index of Erectile Function (for Men).

**Figure: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart**

