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Review Article

Opioids and sexual health: A narrative review

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Abstract

Opioid dependence is the commonest drug dependence after cannabis worldwide. Physiologically, opioids, by their acute effects, cause enhanced sexual performance while used chronically; they cause sexual dysfunction primarily by influencing the hypothalamo-pituitary-adreno-gonadal axis. Men with opioid use had a significantly increased risk of erectile dysfunction with a relative risk of 1.96. Decrease in sexual desire/libido, anorgasmia, premature ejaculation, loss of ability to attain an erection, decreased sexual satisfaction after intercourse, amenorrhoea, anovulation are the critical effects of long-term opioid usage on sexual health. Such effects are also prominent in those on opioid substitution therapy with buprenorphine and methadone. Hence sexual assessment should be an essential part of the evaluation of those on long-term opioids. Also, the sexual dysfunction due to long-term opioid usage should be adequately addressed.

Keywords: Opioids, Sexual health, Opioid use disorder, Male sexual function, Female sexual function

Introduction

Opium compounds are derived from the dried latex obtained from the seed capsules of the poppy plant *Papaver somniferum*. Opioids can be classified as a) natural opioids- those that can be isolated from the latex, e.g., morphine, codeine, b) semisynthetic opioids - derived from the natural opioids, e.g., heroin, oxycodone, and c) synthetic opioids, e.g., fentanyl, methadone. Opioids work by exerting their actions via a range of receptors present in the central nervous system and peripheral tissues. Opioid receptors are divided into three types - μ, κ, and δ receptors. Their actions make them useful as a pain reliever, anti-tussive agents, amongst many other indications.

Records suggest that the use of opium in

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India began in the 9th century AD after trade with Arab started (Sharma and Soc, 1996). A study in 1890 estimated that one in every 12 adults was found to be an opium addict in Odisha (Sharma and Soc, 1996). However, the Government of India in 1950 restricted opium use. Following these restrictions, opium use slowly reduced, and illicit use or prescription abuse has replaced this (Sharma and Soc, 1996). Opioid use disorder is a problematic pattern of opioid use that leads to clinically significant impairment or distress, manifested by at least two of the eleven criteria listed in DSM-5 occurring within 12 months (Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 2013). A similar diagnosis can be made under ICD 10 (The ICD-10-World Health Organization, 1990). Currently, it is estimated that about 5.8 crore people worldwide used opioids as per the UN World Drug Report in 2020 (United Nations Office on Drugs and Labour, 2021). Trends in opioid misuse include the growing prevalence of prescription opioid use and the high mortality burden due to overdose (CDC Injury Center, 2021). In India, the prevalence of opioid use was found to be 2.06%: most commonly heroin (1.14%) followed by pharmaceutical opioids (0.96%) (MSJM, 2019). Prescription drug use is seen to be more common among females (Serdarevic et al., 2017). Sexual side effects of opioid use had been noted as early as the 1500s by Fabriel d'Orta, who, contrary to the popular belief at that time, suggested that opiate use did not improve sexual function but rather was leading to impotence in regular users (Pfaus and Gorzalka, 1987). Even in India, sexual dysfunction has been noted as early as the 1800s in opium addicts in Assam (Katz and Mazer, 2009). In this narrative review, we look to compile the evidence of opioids and its effect on sexual health.

Mechanism

Understanding from animal studies

Chronic opioid use studies in animals show reversible epigenetic changes: down-regulation of POMC gene (precursor of endorphin and ACTH) mRNA activity. 12 different OPRM1(μ opioid receptor) single nucleotide polymorphisms are associated with an increased propensity to develop libidinal side effects (Wang et al., 2012).

Opioids have been noted to have reversible neuroendocrine effects via kappa receptor (Deviche and Moore, 1987). Changes in aromatase and 5α- reductase mRNA expression leading toreduced testosterone levels have been noted with morphine administration in rats (Aloisi et al., 2010). Long term effect of prepubertal morphine administration in rats was shown to inhibit sexual maturation and showed reduced testosterone and luteinizing hormone (LH) levels (Vuong et al., 2010).

Human studies

Findings from animal studies have been primarily replicated in human studies. Human studies implicate that opioids exert this effect through the hypothalamic-pituitary-gonadal axis (Fig. 1). Opioids act on μ-receptors in the hypothalamus and, over time, reduce the release of gonadotrophin-releasing hormone (GnRH), which reduces follicle stimulating hormone (FSH) and LH. Dampened release of these hormones has many downstream effects, including reduction of estradiol and testosterone (Paice et al., 1994; Vuong et al., 2010). It has been suggested that opioids like morphine, through negative feedback, inhibit GnRH synthesis (Seyfried and Hester, 2012).

Hypothalamic-adrenal axis and adrenal

androgen production are disrupted with chronic opioid use. Testosterone and dihydrotestosterone are decreased on account of decreased dehydroepiandrosterone sulphate (DHEAS) production consequent to decreased adrenocorticotropic releasing hormone production from the hypothalamus (Daniell, 2006). Some studies show that chronic opioid use increases prolactin, which in turn induces negative feedback on LH and FSH release (Seyfried and Hester, 2012). This process interferes with the menstrual cycle and libido in women through its effect on estrogen and progesterone. Putatively, opioids being central nervous system depressants, can result in sedation, affecting sexual function (Gulliford, 2016).

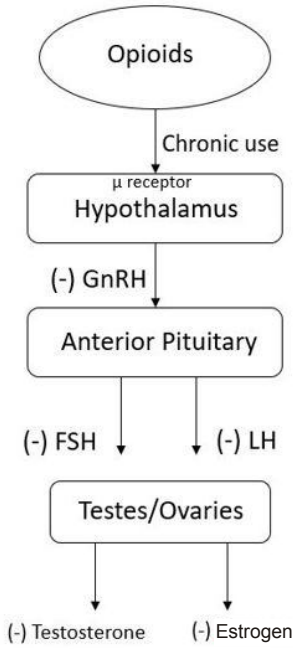

Fig 1: Effect of Opioids on HPG axis

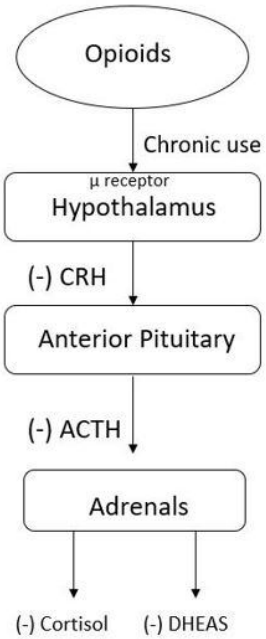

Fig 2: Effect of Opioids on the adrenal axis

GnRH – Gonadotrophin-releasing Hormone, FSH – Follicle-stimulating Hormone, LH - Luteinizing Hormone, CRH – Corticotrophin-releasing Hormone, ACTH - Adrenocorticotropic Hormone, DHEAS – Dehydroepiandrosterone sulfate

Impact on sexual function after short-term use

Commonly, short-term opioids misuse generally as an aphrodisiac during sexual intercourse (Pfaus and Gorzalka, 1987). It had noted that acute use by intravenous injection of morphine was noted to have an orgasmic effect with pleasure centres triggered in the pelvic-pubic area. Contrary to the evidence, men with opioid abuse cited heroin as a solution to their premature ejaculation (Chekuri et al., 2012). Another study in 2007 revealed that current sexual activity was significantly associated with codeine use in sexually active youths (Peters et al., 2007). In women who experienced dyspareunia and vaginismus, relaxation induced by opioids along with their analgesic effect has been useful. An ayurvedic medicine called "Kamini vidrawan ras", sold as a sexual performance enhancer, was found to contain codeine, morphine and papaverine (Kamini). "Barshasha", an Unani

paste preparation primarily for cough, containing opium, has been prescribed for sexual functioning (Basu et al., 2011).

Sexual health and chronic use of opioids

Past reviews report that males with chronic opioid use complain of anorgasmia, delayed ejaculation, erection dysfunction, reduction in sexual dreams, and early morning tumescence. Among female chronic opioid users, studies report anorgasmia, amenorrhea, and an ovulation (Pfaus and Gorzalka, 1987). A study evaluated sexual function and testosterone in patients receiving intra spinal opioids for at least one month. They found that all patients reported a reduction in libido. Other common findings seen were impotence, erectile dysfunction, delayed ejaculation, and reduction in nocturnal emissions. They also found that age was a secondary factor that influenced the effect of the opioid on serum testosterone (Paice et al., 1994).

Males on opioids for chronic back pain reported a higher prevalence of sexual dysfunction (Deyo et al., 2013). They noted that a higher opioid dose (≥120 mg morphine equivalent dose) was an independent factor associated with higher use of medications. In another study of men with chronic non-cancer pain, who received opioids for at least 12 months, 35% reported sexual dysfunction. In 19% of these men, low serum testosterone was found (Ajo et al., 2016). Morphine equivalent dose was found to be correlated to sexual dysfunction intensity. Another study found that sexual dysfunction in all domains of erectile function, orgasmic function, sexual desire, and intercourse satisfaction was seen with long term use of heroin (Zhang et al., 2014). In a meta-analysis that included ten studies encompassing about 2,456 men who received long term opioid management and looked specifically at risk of erectile dysfunction, found that men with opioid use had a significantly increased risk of erectile dysfunction with a relative risk of 1.96 (Zhao et al., 2017). The overall quality of pooled studies was adjudged to be low, but no publication bias was reported. These results have significant implications for medical professionals prescribing opioids.

A systematic review of reproductive side effects in women treated with an opioid for one month or longer for chronic non-cancer pain showed that they were more likely to have signs of hypogonadism. In 10 studies that looked at hormonal assays, only 2 showed a significant decrease in testosterone, estradiol, FSH, LH, and DHEAS. Amenorrhoea was seen in 23-71%, and decreased libido was seen in 61-100%of those receiving opioids (Wersocki et al., 2017). Since both libido and amenorrhoea are linked to fertility, this could be a significant concern for women. The paper summarised that while the studies were limited, shared decision-making with education about sexual side effects is essential when starting long-term opioids in pre menopausal women. In a study looking at women receiving long-term opioids for chronic non-cancer pain, 25% of the women reported sexual dysfunction with effect on lubrication, arousal, orgasm, and sexual satisfaction (Ajo et al., 2016).

Another issue to be considered for sexual dysfunction with opioid medication is that it is often present in combination with other drugs (ASCORIL-C | CIMS India, 2021; ULTRACET | CIMS India, 2021). With their sedative and relaxant effects, Antihistamine drugs can cause sexual dysfunction as histamine has a role in penile erection. Impotence is a common side effect associated with drugs having anticholinergic activity. Acetaminophen and ibuprofen also have been linked to erectile dysfunction.

Most of the studies done in recent years have been about either illicit drugs or prescription drugs. However, this narrative review has found that sexual dysfunction is significantly associated with opioid use in males and females. The summary of the types of dysfunctions has been listed in Table 1.

Opioid substitution therapy

Opioid substitution therapy is an important component in managing opioid use disorder where an opioid agonist, which is relatively safer, is prescribed for a longer-term under medical supervision. The most commonly used medications for long-term maintenance in India are methadone and buprenorphine. Methadone has a similar action to morphine, being a typical opioid receptor agonist and has similar mechanisms for sexual dysfunction. Buprenorphine is a partial agonist at μ receptor and antagonist at the κ receptor site. The mechanism of sexual dysfunction due to its μ receptor might be offset by its antagonist action on the κ receptor.

A study examined the prevalence of sexual dysfunction in opioid-dependent men recruited from a methadone maintenance clinic. 14% of the men reported some sexual dysfunction with increased orgasmic dysfunction directly correlated with methadone dose. The prevalence of sexual dysfunction due to opioid abuse increased with age. Elevated prolactin was the most common endocrinologic abnormality in the study (Brown et al., 2005). A summary article found that sexual dysfunction amongst opioid substitution treatment was more common than in the general population. They estimated the prevalence of sexual dysfunction in methadone-maintained populations to vary between 30-100% (Brown and Zueldorff, 2007).

Amongst those availing methadone maintenance treatment after chronic heroin use, sexual dysfunction reduced in severity after methadone substitution (Zhang et al., 2014). Similarly, in another study, it was seen that even though sexual dysfunction was noted in methadone maintenance treatment, a significant improvement was seen in erectile function, sexual desire, orgasmic function, and satisfaction with it compared to that on illegal drugs (Bagher et al., 2016).

Women on methadone substitution treatment reported sexual side effects such as reduced sexual interest, emotional arousal, orgasm, and vaginal lubrication (Teusch et al., 1995). The risk of menopause and menstruation abnormalities was seen to be increased in long-term female opioid users and methadone maintenance clients (Richardson et al., 2018). A recent study found that 56.6% of the women receiving at least three months of opioid substitution treatment showed sexual dysfunction (Zamboni et al., 2019). Another study that examined patients on maintenance therapy and its effect on sex hormones and sexual function found that in those treated with buprenorphine, 23% reported reduced libido and 12% reported reduced potency, while those on methadone, 83% reported reduced libido and 72% reported reduced potency. Mean testosterone levels were lower in methadone-treated patients compared to buprenorphine and controls. Mean levels of prolactin were significantly higher in the methadone group than in the buprenorphine group (Bliesener et al., 2005).

Another study found a significant association between erectile dysfunction and maintenance treatment. They noted that those on buprenorphine therapy reported less erectile dysfunction than methadone (Quaglio et al., 2008). Other factors contributing to erectile dysfunction include comorbid depression and heroin use by partners.

Studies have convincingly shown that sexual dysfunction is seen in patients both on methadone and buprenorphine. Despite this, it has been shown that opioid substitution therapy is still beneficial compared to patients on illicit opioids/ prescription opioids. Psycho education and assessment for sexual dysfunction are crucial components of the long-term management of patients on opioid substitution.

Table 1. Sexual dysfunction in opioids and opioid substitution therapy

Drug	Male	Female
Opioids-Illegal or prescription	Decrease in sexual desire/libido Anorgasmia Premature ejaculation Loss of ability to attain an erection Loss of ability to maintain an erection Decrease in sexual satisfaction after intercourse	Decrease in sexual desire/libido Anorgasmia Amenorrhoea Anovulation Decrease in sexual arousal Decreasedvaginal lubrication
Buprenorphine or Methadone (OST)	Premature ejaculation Loss of ability to attain an erection Loss of ability to maintain an erection Decrease in sexual desire/libido	Menstrual abnormalities Decrease in sexual desire/libido Decrease in arousal Decrease in orgasm and vaginal lubrication

Opioid antagonists

Naloxone, Nalmefene, and Naltrexone are pure opioid antagonists with actions on all three opioid receptors. Naloxone is mainly used as the drug of choice for opioid overdose, where as naltrexone is used for the management of opioid and alcohol use disorders for craving and heavy use. In 1977, a study measured the changes in LH, FSH, and prolactin in male rats when injected with morphine, met-enkephalin, and naloxone. They found that morphine and met-enkephalin increased prolactin and reduced LH and FSH secretion, reversible with naloxone (Bruni et al., 1977). Various studies in animals have shown that opioid antagonists like naloxone and nalmefene acutely increased LH and testosterone (Estienne et al., 2009; Tenhola et al., 2012; Hernandez et al., 2016). Human studies related to naloxone usually include the buprenorphine combination. A study showed that the effect of buprenorphine was prominent over naloxone, with patients reporting sexual dysfunction (Mattoo et al., 2021).

Studies have shown that patients on naltrexone treatment have a high prevalence of sexual dysfunction (Venkatesh et al., 2014; Bliesener et al., 2005). Complaints commonly seen were premature ejaculation, erection dysfunction and reduction in sexual desire. However, some studies investigating Naltrexone being an opioid antagonist have the opposite

effect on sexual function than opioids. In another study, male patients with impotence were given Naltrexone daily for two weeks and were compared with those who were given a placebo. They found that naltrexone therapy significantly increased the number of successful coitus, improved spontaneous erection, and improved sexual performance compared to placebo (Fabbri et al., 1989). A study that looked at Naltrexone-induced augmentation of sexual response in men found that they experienced a significantly greater number of orgasms and intensity of arousal and orgasm while on the drug (Sathe et al., 2001).

In summary, opioid antagonists have the opposite effect on sexual function, with most studies showing the improvement in sexual function. Therefore, Naltrexone may be a promising drug of choice for relapse prevention in patients with sexual dysfunction.

Indian studies

The opioid is the most commonly used substance in India after alcohol and cannabis. The 2017 survey showed that prevalence being higher than earlier survey and that heroin surpassed opium use. The prevalence of injection opioid use was 8.5 lakh people (MSJE, 2019).

A study showed that sexual dysfunction was seen in 48% of the dependent group compared to only 8% in the control group. 74% of the opioid-dependent group reported sexual dysfunction in the form of decreased sexual satisfaction, and 45% reported erectile dysfunction. The study also showed that the opioid-dependent group had a significantly higher prevalence of dysfunction in domains of desire, arousal, and orgasm (Venkatesh et al., 2014).

A study found that 53% of males with opioid dependence reported sexual dysfunction. Most prevalent dysfunction was in the domain of desire (63%), erection (50%), orgasm (48%), and satisfaction (43%). They also noted that the average duration between the onset of dependence and the onset of sexual dysfunction was about 11 months (Aggarwal et al., 2016). Looking at studies related to opioid substitution therapy and opioid antagonists, 83% and 90% of those receiving buprenorphine and Naltrexone respectively reported at least one sexual dysfunction symptom. Most commonly reported in buprenorphine and naltrexone groups were premature ejaculation, erectile dysfunction, and reduction in sexual desire (Ramdurg et al., 2011).

Another study in Chandigarh compared 40 men on six months of opioid substitution therapy with buprenorphine/naloxone combination with healthy controls for sexual dysfunction. They found that men on opioid substitution reported higher rates of sexual dysfunction with mainly intercourse dissatisfaction (95%), hypoactive sexual desire (92.5%), erectile dysfunction (77.5%), orgasmic dissatisfaction (53%), and ejaculatory dysfunction (45%) (Mattoo et al., 2021).These studies show that sexual dysfunction is seen in Indians with opioid use disorders and those on opioid substitution treatment. However, lack of studies on female opioid users was noticed. The studies showed sexual dysfunction variety to be similar to that seen in the earlier international studies, as summarised in Table 1.

Management

Management of opioid use-related sexual dysfunction begins with a detailed assessment of premorbid and current sexual functioning. Specific structured assessment tools such as the International Index of Erectile function (IIEF), Arizona Sexual Experience Scale (ASEX), Female Sexual

Function Index (FSFI), Index of Sexual Satisfaction (ISS), Orgasm Rating Scale (ORS), Index of Premature Ejaculation (IPE) and Dyadic Adjustment Scale (DAS) can provide further insights. Aside from routine investigations, hormonal assays like serum LH, FSH, testosterone, and prolactin should be done.

In cases of erectile dysfunction, phosphodiesterase inhibitors like sildenafil and tadalafil have been used with some improvement. Testosterone replacement therapy has been shown to ameliorate opioids related sexual dysfunction (Hsieh et al., 2018). Testosterone is available in either intramuscular form (75-100mg/week or 150-200mg/2 weeks), transdermal patches (5mg patch or two every night), testosterone gel (30-120mg daily), and testosterone pellets which can be implanted subcutaneously. Transdermal patches have been used in women with low serum androgens and have shown improvement in libido and sexual response. Adverse effects of testosterone replacement in men include priapism, azoospermia, and gynecomastia. Frequent monitoring and evaluation for cardiac and prostate issues are indicated. Bupropion with a 100-300mg dose for 6-8 weeks for sexual dysfunction in opioid substitution therapy has shown benefit in some studies (Tatari et al., 2014; Salehi et al., 2015). A randomised, double-blind control trial reported improvement in erectile function, sexual desire, intercourse satisfaction, and overall sexual function with bupropion treatment (Yee et al., 2018). In herbal medication studies, both Rosa damascene and ginseng have been studied. They have shown improvement in sexual function in desire, arousal, orgasm, and overall sexual function in both males and females (Farnia et al., 2017, 2019). Bromocriptine is another alternative drug suggested in patients with prolactin dysfunction with its action on CNS level dopamine and hence dopamine-mediated regulation of prolactin (Brown and Zueldorff, 2007).

Review limitations

This is a narrative review on opioids and its sexual side effects. We note that recent studies report greater use of heroin and prescription opioids. We noticed that most of the studies were retrospective studies or cross-sectional studies looking at prevalence. The studies also had limitations that sexual function is very subjective with external factors like stress, relationship with the partner, and mental health comorbidities common in opioid use disorders having an effect. We also noticed that very few studies evaluated sexual dysfunction in women. Indian studies examining this were also few, mainly concentrating on heroin and those on opioid substitution. Studies in other minority populations involving age, gender, and sexual orientation were not found by the authors. These gaps should be filled by future research on this topic in these populations.

Conclusion

This is not a systematic review, but it is clear from the evidence above that opioid-induced sexual dysfunction is a common effect of long-term use of opioids and must be part of the history collected in cases of opioid use disorder. Opioid use in the long term is related to sexual dysfunction by the above mechanisms. As most studies had a study duration of at least six months, we can conclude that sexual dysfunction can arise as early as six months of opioid use. However, no robust review or systematic review informs the mean duration to the onset of sexual side effects. Studies also show that the dosage of opioids is related to the incidence of sexual dysfunction, with a reduction in opioids showing improvement (Rajagopal and Bruera, 2003). Sexual and erectile dysfunction are often linked with the quality

of life as one of the essential components of quality life measure is satisfaction with sex life (Ajo et al., 2016; Yee et al., 2018). This effect can be used as a motivation to prevent relapse. Sexual dysfunction due to substitution treatment is distressing and may lead to non-compliance, which increases the likelihood of relapse. Hence this is a critical topic to keep in mind. However, as the above literature shows, even for sexual side effects, either buprenorphine /methadone substitution is better than harmful use or dependence on illicit opioids. Naltrexone studies have shown mixed results with some describing similar dysfunction and some showing improvement.

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