

Review Article



The complications of tramadol and methadone use to women's sexual hormone

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Abstract

Background and aims: Tramadol and methadone are synthetic opioid drugs that are widely used in various fields of medicine. This review article was performed to investigate the hormone disturbance of long-term tramadol and methadone use in women.

Methods: Keywords were determined using the MeSH browser and then searched in ISI, Scopus, EMBASE, and PubMed databases on 25.5.2022. The articles with non-English language, articles whose full text was not retrieved, and studies that were irrelevant to the aim of this study were excluded from the investigation.

Results: Methadone and tramadol affected a sexual hormone in women through an impact on the hypothalamic-pituitary-gonadal axis. They could reduce the levels of follicle stimulating hormone and luteinizing hormone, increase prolactin production, and finally, reduce gonadal steroids. Opioids also could influence thyroid and adrenal glands and subsequently increase thyroid-stimulating hormone, and reduce dehydroepiandrosterone. Eventually, this mechanism caused a disturbance in sexual hormone disturbance in women.

Conclusion: Overall, long-term methadone and tramadol consumption as opioid substances could cause sexual hormone disturbance in women.

Keywords: Methadone, Tramadol, Sexual, Sex hormone, Women

Received: July 13, 2022 Accepted: August 6, 2022 ePublished: May 1, 2023

Introduction

Sexual health in women profoundly affects general health, communication, intimacy, and marriage (1). The presence of any problems in the field of sexual performance may lead to negative effects on general well-being and overall quality of life (2). Drug abuse among women is one of the factors that endangers married life. Today, due to the progress of science, especially in the field of pharmaceutical and synthetic products, the problem of complications and poisoning caused by the use of drugs has become a highly important issue, especially among the Iranian population (3). Tramadol and methadone are among the most commonly used drugs. Nowadays, methadone is abused so much that at least a hundred patients are poisoned every day due to the unintentional use of this drug and arbitrary consumption of more than recommended by the doctor, as well as a lack of knowledge of the drug's pharmacokinetics (4). Although one of the most common methods for addiction treatment is methadone maintenance treatment, it also has other

uses, including relieving chronic and severe pain (5). The high accumulation of methadone in fat tissue and its slow metabolism have caused the long-lasting effect of this drug compared to other morphine-based opioid drugs (6). Suicide attempts are the main cause of overdose of this drug (7). In addition, tramadol is used to relieve moderate and severe pain and chronic pain such as joint and bone pain, nerve pain, back pain, and cancer pain (8,9). The main tramadol overdose complications are seizure, hypertension, and tachycardia (10-12). Generally, the overdose of tramadol and methadone leads to polydrug use-associated deaths (13). However, the sexual side effects of these drugs in women have received less attention from medical researchers. The most important symptom of androgen deficiency caused by drugs is sexual dysfunction of both sexes, which affects about 76% of men and about 64% of women (14). There are many questions about the unwanted effects of these drugs on the structure and function of different organs of patients. The reproductive system is one of the organs of

the woman's body that is sensitive to its function. Some review studies show that the use of methadone and tramadol can have extensive sexual hormone disturbance, endocrine abnormalities, and the reproductive health of women (15-17). Generally, the research examining the effects of opioid abuse on sexual hormones in females is limited. Considering the importance of women's health on the health of the family and society and given that few studies have been conducted on the effect of methadone and tramadol on women's sexual health, the present study aimed to evaluate the adverse effects of tramadol and methadone drugs on women's sexual hormone.

Materials and Methods

In this narrative review, an extensive search was performed on 25.5.2022 in Scopus, PubMed, EMBASE, and Web of Science (ISI) databases using different keywords. They included ((“sexual health“ OR “sexual hormone” OR “estrogen” OR “progesterone” OR “prolactin” OR “follicle-stimulating hormone” OR “luteinizing hormone”) AND (“synthetic opioid” OR “opioid analgesics” OR “methadone” OR “tramadol”). Additional searches were conducted on previous reviews and studies, but no additional studies were found in this regard.

Duplicate studies were removed in EndNote X8 software (November 8, 2016, Thomson Reuters), and a re-control of the remained studies was performed. After removing studies unrelated to the purpose of the study, two researchers independently screened the content of the title and abstract of the selected articles based on the inclusion and exclusion criteria and the studies that met the inclusion criteria. Then, based on the inclusion criteria, studies that addressed the effect of methadone and tramadol on women's sexual hormones were included in this systematic review.

Results

Opioids, including methadone and tramadol, cause hormonal disorders in women. In women, disturbances in estradiol and progesterone lead to amenorrhea, oligomenorrhea, anovulation, and finally infertility (18). Opioid-induced hypogonadism (OHG) is one of the complications of long-term (more than 4 weeks) opioid therapy. OHG is associated with a disturbance in hypothalamic gonadotropin-releasing hormone (GnRH) secretion with the consequent deficiency of follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, and estrogen (19). Some studies demonstrated that OHG potentially leads to hypogonadism oligomenorrhoea and mainly causes decreased libido and infertility in premenopausal women (20,21).

The following section discusses some hormonal disorders caused by methadone and tramadol in women.

Methadone

Methadone is one of the drugs whose side effects depend on the dose and length of exposure (22). Declined levels

of sex hormones after opioid consumption were described in patients during methadone maintenance and abusing heroin (23,24). Evidence indicates that methadone disrupts the serum level of different sex hormones in women, and their sexual performance faces various problems.

Effect of methadone on prolactin

Human immunodeficiency virus-infected female methadone users show low serum prolactin levels compared to the control group (25). Spagnolli et al reported that women receiving methadone have increased prolactin basal concentration in comparison to the control group (26). Unlike the effects of opioids on growth hormone, their effects on prolactin secretion are significantly different in men and are influenced by the timing of opioid use, particularly in the female cycle (27). Rolandi and Barreca found that females affected with breast cancer when using methadone represented immediate elevations in serum prolactin levels following administration (28). Trajanovska et al indicated that methadone can increase plasma prolactin levels in the methadone maintenance therapy group (15). The results of a study revealed that opioid addiction treatment with methadone during pregnancy may continue into breastfeeding, but the infant situation should be monitored carefully (29).

Effect of methadone on luteinizing hormone and follicle stimulating hormone

Methadone therapy for opioid abuse does not change FSH levels in pre- and post-menopausal females (30). Psychoneuroendocrinology consuming prescribed sustained-action opioids in women receiving opiate drug treatment for pain management, including methadone, lead to reductions in FSH levels, whereas FSH levels in pre-menopausal females are not changed from premenopausal controls. Thus, 70% of women consuming prescribed sustained-action opioids such as methadone have lower FSH (31).

Bonakdaran et al found that methadone treatment for opioid abuse in menopause women does not alter LH levels compared to controls without methadone (30). According to another study, in women who consumed prescribed sustained-action opioids (including methadone) for control of nonmalignant pain, LH levels decreased compared to control pre- and post-menopausal females, and more significant effects were observed in post-menopausal women. Methadone consumption of 35-200 mg/d in non-cancer pain can reduce LH levels (31).

Effect of methadone on estrogen

Serum samples from females receiving methadone for pain management revealed no changes in estradiol levels compared to control group samples (32). Bonakdaran et al reported that methadone has no significant effect on estradiol levels in women receiving methadone therapy for opioid abuse (30). However, another study indicated that estradiol levels reduce in menopausal women

receiving methadone for chronic pain in comparison to the pre-menopausal control group (31). In pregnant women who had taken methadone illegally, estriol levels in the third trimester were decreased compared to pregnant controls (33).

Tramadol

Tramadol also shows gonadotoxic effects on tramadol-dependent alterations and human hormone levels. Its manner depends on the dose and time of consumption (34,35).

Effect of tramadol on prolactin

Tramadol can increase women's serum prolactin (36). However, no difference in breastfeeding rates was observed among mothers with established lactation and patients who received naproxen for post-cesarean section pain (37). The other proposed mechanisms may include increased prolactin or decreased dehydroepiandrosterone (DHEA), which is an important precursor of testosterone (16). The findings of one study represented that postpartum prolactin levels were significantly higher in the tramadol group than in the sufentanil group, and there was a significant delay in the initiation of breastfeeding in the tramadol group (38).

Effect of tramadol on luteinizing hormone and follicle stimulating hormone

Tramadol abuse leads to decreased release of gonadotropin-releasing hormone or modification of its pulsatility, resulting in the decreased release of LH and FSH from the pituitary, and consequently decreased gonadal steroid production (16). Another study also reported reductions in the levels of FSH, LH, progesterone, and estrogen (39). In their study, Abdel-Hamid et al concluded that tramadol abuse leads to decreased release of LH, and consequently decreased gonadal steroid production (16).

Effect of tramadol on estrogen

To the best of our knowledge, no human study was found in this regard. A study showed that tramadol in 100 mg/kg body weight can reduce the estrogen serum level in mice (39).

In fact, tramadol and methadone cause damage to fertility and sexual disorders in several ways. First, it inhibits the secretion of sex hormones from the hypothalamus. In this mechanism, the pituitary gland no longer produces its two sex hormones and causes no egg release. The second mechanism is that methadone increases blood prolactin hormone, thus prolactin inhibits hypothalamus function. The third one is that methadone itself has direct toxic effects on the gonads and causes a decrease in their activity (22).

On the other hand, DHEA-dehydroepiandrosterone sulfate (DHEAS) deficiency also has a substantial role in sexual dysfunction. DHEA levels decreased during the consumption of sustained-action prescribed opioids such

as methadone consumption (40).

Discussion

This review was performed to investigate the hormone disturbance of long-term tramadol and methadone use in women.

In this study, methadone and tramadol disturbed sexual hormones in women through an effect on the hypothalamic-pituitary-gonadal axis and thyroid hormone and reduced the levels of FSH and LH, increased prolactin production, and finally, reduced gonadal steroids. A review article reported that despite its effectiveness in managing substance abuse and treating chronic pain, methadone has adverse effects on the hypophysis-hypothalamus gonadal axis and sexual function in women. However, to draw stronger results, more studies are needed in this field (22). Another study investigated the adverse effects of methadone and buprenorphine on types of sexual disorders, sexual desire, erection, and orgasm disorders, which most patients face during drug replacement therapy (41). Trajanovska et al showed that sexual dysfunction in examination groups' sexual desire and overall satisfaction did not represent a change, while significant changes were observed in erectile and orgasm function (15).

Fertility is one of the most important issues for every woman. Unfortunately, opioid abuse has a negative effect on women's fertility. Recent studies have demonstrated a decrease in the level of sex hormones due to the use of methadone and multiple effects of methadone on the endocrine system, including the possibility of hypogonadism (22,27).

The hypothalamus secretes hormones through the blood flow, by affecting the pituitary gland, it causes the release of two sex hormones, FSH and LH, from the pituitary gland. These two hormones affect the ovaries and cause the production of estrogen and progesterone and ovulation. Evidence suggests that opioids, both endogenous and exogenous, which are prescribed for chronic pain and illegal usage, mainly affect ovarian activity by binding to opioid receptors in the hypothalamus and then the pituitary gland. By reducing GnRH secretion at the level of the hypothalamus, opioids disrupt its pulsatile function, causing a decrease in FSH and LH, leading to hypogonadotropic hypogonadism (42).

In general, opioids preferentially act on different receptor sites, leading to either stimulatory or inhibitory effects on hormone secretion. Long-term use of opioids mainly increases prolactin while decreasing oxytocin, LH, and estradiol. The main consequences of hypogonadism in women include oligomenorrhea, amenorrhea, decreased libido, and loss of bone tissue or infertility (27).

Although most conducted studies emphasized the effective role of tramadol and methadone in hormonal disorders and sexual function, there are reports of the lack of the effect of opioid compounds on sexual hormones. For example, Wong et al reported that hormone levels did not correlate with the frequency of sexual dysfunction in

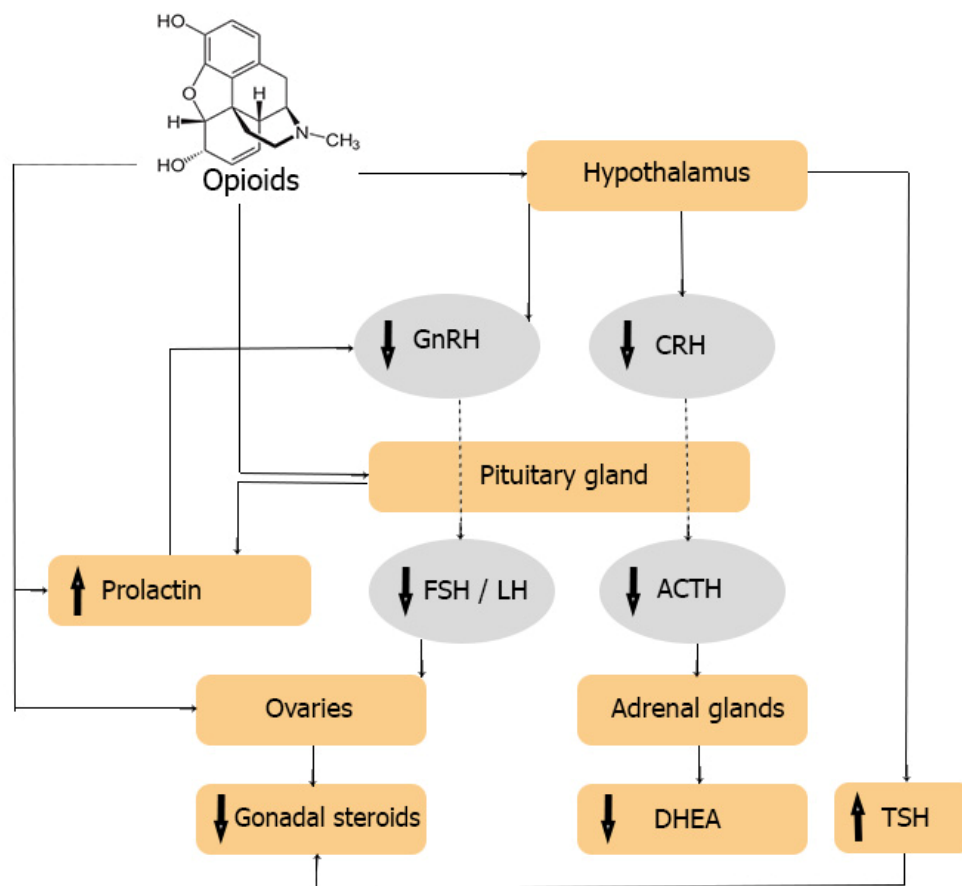


Figure 1. Methadone and tramadol mechanisms affecting hormone secretion. Note. CRH: Corticotropin-releasing hormone; GnRH: Gonadotropin-releasing hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; ACTH: Adrenocorticotropic hormone; DHEAS: Dehydroepiandrosterone sulfate; TSH: Thyroid-stimulating hormone

women taking opioids. Women on opioids had lower free testosterone levels, but this was not associated with sexual dysfunction (43). Generally, the effect of methadone and tramadol on the hypothalamic-pituitary-gonadal axis and TSH is illustrated in Figure 1.

By having the direct effect of methadone on the hypothalamus, opioids bring forth an alteration in normal gonadotropin pulse patterns, along with a selective effect of methadone on the anterior pituitary, which alters its response to GnRH, with either mechanism leading to a reversible, dose-related depression of testosterone levels (44). Overall, sexual dysfunction among women on opioid therapy appears to be mainly associated with interference in the normal cyclic secretion of LH and FSH, possibly due to the increased production of prolactin cause (41).

In addition, opioids can disrupt the function of thyroid function by decreasing T3RU while increasing total T3 and free T4 levels and TSH (45,46). Opioids increase TSH and lead to thyroid gland disorders. The increase in the abuse of opioid substances leads to hypogonadism in the first stage, but it may also affect the secretion of other pituitary hormones. This disturbance in thyroid hormones can reduce gonadal steroid production (27).

The limitation of the review studies was the selection and allocation failure. Deficiencies in the implementation method, lack of control of potential confounding, factors, and bias assessments were observed as well.

Conclusion

Overall, the long-term consumption of methadone and tramadol affected the hypothalamic-pituitary-gonadal axis and thyroid hormone, leading to increased prolactin production, reduced levels of FSH and LH, and finally decreased gonadal steroids. Opioids could also influence thyroid and adrenal glands, subsequently increasing TSH while reducing DHEA. Therefore, methadone and tramadol through this mechanism caused sexual hormone disturbances in women.

Additional rigorous well-designed studies should be performed for the potential long-term risks of methadone and tramadol risks for sexual health in the women population.

Authors' Contribution

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Competing Interests

The authors declared no conflict of interests, financial or otherwise.

Ethical Approval

Not applicable.

Funding

None.

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