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The Effect of Methadone on the Hypothalamic Pituitary Gonadal Axis and Sexual Function: A Systematic Review

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Review

The effect of methadone on the hypothalamic pituitary gonadal axis and sexual function: A systematic review

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ABSTRACT

Background: Opioid abuse is a public health crisis. As opioid misuse worsens, efforts are being made to increase access to medication-assisted treatments. Methadone is a medication-assisted treatment used to treat opioid dependence and chronic pain. While methadone is beneficial in the treatment of opiate abuse and chronic pain, side effects of the medication include hormonal and sexual function changes. The purpose of this report is to review the effects of methadone on the hypothalamic pituitary gonadal axis hormones and sexual functioning in males and females.

Methods: A search of PubMed was conducted using pre-defined criteria, resulting in the evaluation of 295 articles. A total of 72 articles, including 52 human studies and 20 animal studies, met the selection criteria and were reviewed. The included studies examined the effects of methadone on the hypothalamic pituitary gonadal axis and/or sexual function.

Results: There was evidence of methadone-induced hormonal changes, disruptions in the hypothalamic pituitary gonadal axis, and sexual dysfunction, although there was some variability in the results of the reviewed studies. Differences in methadone dose and length of exposure to treatment appears to influence the variability in the results. Much of the literature examines the effects of methadone in males, with very limited research examining the effects in females.

Conclusions: Despite its effectiveness for opiate abuse and chronic pain treatment, methadone has disruptive effects on the hypothalamic pituitary gonadal axis and sexual function. Further research is warranted to better define potential methadone-induced endocrine consequences and to further examine the effects of methadone in females.

1. Introduction

Opioid dependence and opioid overdose deaths are a public health crisis in the United States, with more than 115 Americans dying of opioid overdoses per day (CDC, 2018). In 2018, synthetic opioids accounted for 59.8 % of all opioid overdose deaths, a 45.2 % increase from 2017 (CDC, 2018). According to the National Survey on Drug Use and Health (NSDUH), 11.4 million people aged 12 or older misused opioids in 2017, the vast majority of whom (11.1 million) misused prescription pain medications for the primary reason of relieving pain (SAMHSA, 2018). As the opioid epidemic continues to worsen, efforts are being made to expand access to medication-assisted treatment and harm reduction services.

Methadone is therapeutically used to treat opioid dependence and manage chronic pain. Methadone is a synthetic μ-opioid receptor agonist (Garrido and Troconiz, 1999). Methadone has a lower affinity for μ-opioid receptors compared to other opioids (for review, see (Garrido and Troconiz, 1999)) but has a substantially longer half-life of 23–26.8 h (Wolff et al., 1993). Despite these beneficial uses of methadone, it can still be illicitly abused. However, methadone has one of the lowest rates of misuse compared to other opioids, with only 0.1 % of people aged 12 or older misusing methadone (SAMHSA, 2018).

Opioids, including methadone, affect the hypothalamic pituitary gonadal (HPG) axis, although the precise mechanism of these effects remain unclear. The HPG axis is regulated by a negative feedback mechanism. In response to low circulating levels of testosterone (in males) or estradiol (in females), the hypothalamus releases gonadotropin releasing hormone (GnRH), which acts on the anterior pituitary to secrete luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Plant, 2015). After being secreted into the bloodstream, LH and FSH bind to receptors in the testes (in males) and ovaries (in females), which subsequently increase the release of testosterone (in males) and

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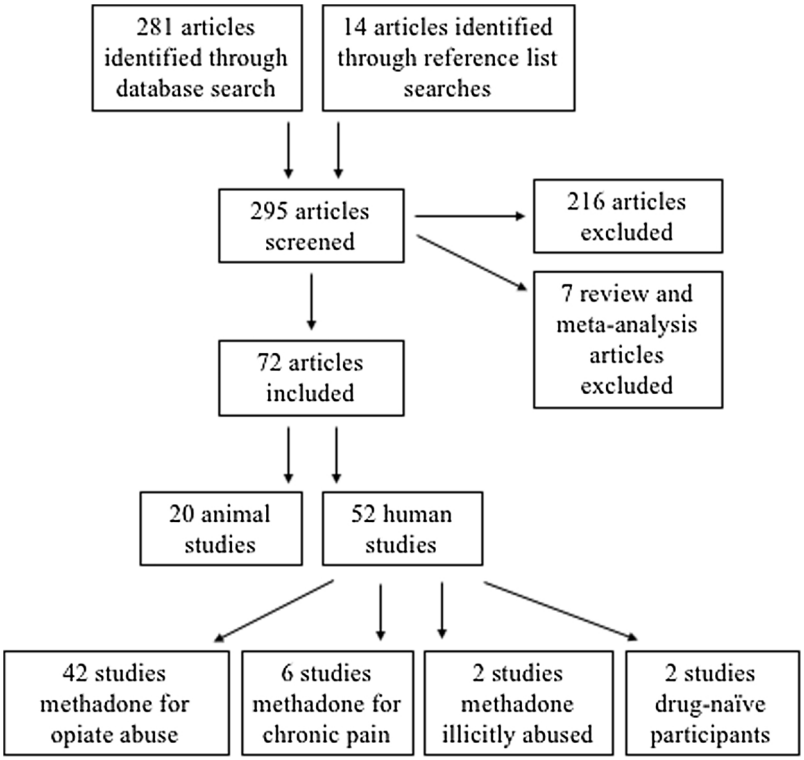

Fig. 1. Flowchart of identification and screening process for included articles (Moher et al., 2009).

estrogens and progesterone (in females) (for review, see (Smith and Elliott, 2012)). Testosterone and estrogens and progesterone act as negative regulators by indirectly inhibiting further GnRH release in the hypothalamus (Plant, 2015) as well as inhibiting LH release in the anterior pituitary (Shaw et al., 2010). Prolactin is a hormone with a variety of functions that is secreted from the anterior pituitary and can indirectly inhibit GnRH release from the hypothalamus (for a review, see (Grattan, 2015)).

Sex hormones and the HPG axis play an important homeostatic and physiological role in modulating sexual behavior. Opiate-induced alterations in the HPG axis can result in hypogonadism and changes in sexual function. While these symptoms may improve over time, studies show that methadone-induced sexual disorders are common (for meta-analysis review, see (Babakhanian et al., 2017)), and may be problematic for individuals initiating methadone treatment. It remains unclear whether these alterations occur at the level of the hypothalamus and pituitary gland or via direct action on secondary reproductive sex organs and the gonads (testes or ovaries). Moreover, these alterations may be sex-specific. In the context of the current opioid crisis in the United States, it is important for clinicians and scientists to be aware of the potential effects of methadone on HPG axis and sexual function to inform the best treatment for patients.

Previous reviews have examined the effects of opioids, including methadone, on the endocrine system and sexual functioning (Bawor et al., 2015; Colameco and Coren, 2009; Katz and Mazer, 2009; Smith and Elliott, 2012; Thomas et al., 1977; Varma et al., 2018; Yee et al., 2014). To the best of our knowledge, no reviews have examined the effects of methadone on the HPG axis and sexual function in both males and females. Furthermore, more recent reviews have focused on other opiate drugs such as buprenorphine. This review examines the literature on methadone's effects on the HPG axis and sexual function in males and females.

2. Methods

2.1. Search strategy

PubMed was searched for peer-reviewed articles in English using two sets of keywords: (1) methadone, (2) sex differences, sex hormones, sex steroids, gonadal steroid hormones, testosterone, estrogen, estradiol, estriol, follicle-stimulating hormone, luteinizing hormone, prolactin, progesterone, sexual function, secondary sex organs. Boolean indicator "or" was used between the terms in the second set of keywords, and Boolean indicator "and" was used between the first and second set of keywords. We additionally searched the reference lists of included articles to scan for any relevant studies that may have not populated during our initial search. The last literature search was completed in May 2019.

2.2. Inclusion and exclusion criteria

Articles examining humans or utilizing animal models that investigated the effect of methadone on the HPG axis or sexual function and met the following criteria were included for this review: observational studies (i.e., cohort, cross sectional, case control, case crossover), or interventional studies (i.e., pre-post, non-randomized trial, randomized controlled trials). There were no restrictions based on demographic measures or the duration of methadone treatment. Included studies were ones that: compared methadone users to non-methadone control groups; studies that compared hormone values of methadone users to the corresponding standard reference ranges; within-subject studies that compared before and after initiation of methadone use; and studies that measured percentage of occurrence within methadone users. Excluded studies were ones that: were case studies; were uncontrolled trials; compared methadone users to another opioid (e.g., heroin) or drug using groups; studies where the effect of hormone manipulation on opioid efficacy was measured; and studies without any quantitative comparisons using statistics. Review articles and meta-analyses were read and reference lists searched for additional articles to

include. However, review articles and meta-analyses were not included as counted articles. Based on these criteria, a total of 295 articles were reviewed and 216 research articles and 7 review/meta-analysis articles from the search were excluded (Fig. 1).

2.3. Data screening

Articles were title and abstract screened for relevance using the aforementioned inclusion criteria. Identified relevant articles underwent further full text analysis. Authors conducted the literature search, screening, and data extraction independently; disagreements at any phase of the literature review and screening process were resolved by discussion. This systematic review follows the guidelines laid out in the Preferred Reporting Items for Systemic Reviews and Meta-Analyses: The PRISMA Statement (Moher et al., 2009).

3. Results

3.1. Screening results

A total of 72 articles were identified for inclusion (Fig. 1). Of the 72 articles reviewed, 52 were human studies; 42 investigated therapeutic methadone use for treatment of opioid abuse (Table 1), 6 investigated therapeutic methadone use for chronic pain (Table 2), 2 investigated illicit methadone use (Table 3), and 2 examined the effects of methadone in methadone- and drug-naïve participants (Table 3). Of the 72 articles reviewed, 20 were animal studies (Table 4).

3.2. Prolactin

Studies examining methadone's effect on prolactin levels produce conflicting results. Men receiving methadone treatment for opioid abuse show no differences in prolactin levels compared to controls without methadone (Hallinan et al., 2007; Ragni et al., 1988), or compared to the medically accepted standard ranges of prolactin (Brown et al., 2005; Hallinan et al., 2008; Spring et al., 1992; Trajanovska et al., 2013). In addition, men receiving methadone for treatment of opiate abuse do not show any acute changes in prolactin concentration before or after their regularly scheduled doses of methadone (Cushman and Kreek, 1974). Other research, however, has found that men receiving methadone treatment for opioid abuse show increased prolactin levels compared to controls without methadone (Gerra et al., 2016; Willenbring et al., 1989; Woody et al., 1988) and compared to standard reference ranges (Lafisca et al., 1981). Similarly, two 10 mg doses of methadone increase serum prolactin levels in men diagnosed with mania (Judd et al., 1982). Studies reporting the effects of methadone on prolactin levels in women are limited. Spagnolli et al. (1987) show that women receiving methadone for opioid abuse have increased serum prolactin levels compared to controls (Spagnolli et al., 1987). HIV-infected women on methadone for opiate abuse show low serum prolactin levels compared to controls (Cofrancesco et al., 2006), whereas women diagnosed with breast cancer using methadone for pain management show immediate increases in serum prolactin levels following administration of methadone compared to baseline levels (Rolandi and Barreca, 1978).

Exposure to methadone at various doses increases prolactin levels in male and female rat pups (Kuhn and Bartolome, 1984, 1983), young adult male rats (Clemens and Sawyer, 1974), and adult male and female rats (Bartolome and Kuhn, 1983; Kuhn and Bartolome, 1983). Similarly, a lower acute dose of methadone (1 mg/kg) increases prolactin levels in adult male rats compared to controls (Shaar and Clemens, 1980). Chronic methadone exposure (5 mg/kg/day for 20 days) has no effect on prolactin levels compared to controls in adult male rats (Kuhn and Bartolome, 1985). However, when the methadone dose is increased by 1 mg/kg each day for 20 days, prolactin levels significantly decrease on days 10 and 20 in young adult male rats (Kuhn and Bartolome, 1985). Exposure to methadone during pregnancy in monkeys does not alter prolactin levels compared to controls (Hein et al., 1991).

3.3. Follicle-stimulating hormone

FSH levels are not altered compared to controls or standard reference ranges in men receiving methadone treatment for opioid abuse (Hallinan et al., 2007; Ragni et al., 1988; Spring et al., 1992), or in methadone-naïve men (Delitala et al., 1983). In addition, men receiving methadone for treatment of opiate abuse do not show any acute changes in FSH concentration before or after their regularly scheduled doses of methadone (Cushman and Kreek, 1974). In contrast, other studies show that men receiving methadone for opioid abuse exhibit decreased FSH levels compared to standard reference ranges (Lafisca et al., 1981) or increased FSH levels compared to controls (Bonakdaran et al., 2016). The discrepancy in the effects of methadone on FSH levels between these studies could be due to the concurrent drug use in the Lafisca et al. (1981) study. In men receiving opioids, including methadone, for pain management, there are no differences in FSH levels compared to controls without methadone (Rajagopal et al., 2004). Similarly, men illicitly using methadone show no differences in FSH compared to controls, although 33 % of the sample show elevated FSH levels compared to the normal range for men of a similar age (Azizi et al., 1973).

The research examining the effects of methadone on FSH levels in women is limited. Methadone treatment for opioid abuse does not alter FSH levels in pre- and post-menopausal women compared to controls without methadone (Bonakdaran et al., 2016). Post-menopausal women receiving opiate drug treatment for pain management, including methadone, show decreased FSH levels compared to post-menopausal control women, whereas FSH levels in pre-menopausal women are not altered from pre-menopausal controls (Daniell, 2008). However, it is important to note in this study that methadone was one of multiple opiate drug treatments that were used for pain management and the specific effects of methadone alone cannot be ascertained.

FSH levels are not altered in adult male rats chronically exposed to varying doses of methadone in drinking water for 14 days compared to vehicle controls (Ghowsi and Yousofvand, 2015). FSH levels are decreased in adult female mice exposed to 10 mg/kg/day of methadone for 15 days (Bui et al., 1983a).

3.4. Luteinizing hormone

The literature examining the effects of methadone on LH levels in men and women shows conflicting findings. For example, in men receiving methadone treatment for opioid abuse, LH levels are not reduced from control levels or standard reference ranges (Bonakdaran et al., 2016; Cushman, 1972, 1973; Hallinan et al., 2008; Lafisca et al., 1981; Ragni et al., 1988; Spring et al., 1992). In addition, men receiving methadone for treatment of opiate abuse do not show any acute changes in LH concentration before or after their regularly scheduled doses of methadone (Cushman and Kreek, 1974) or any changes in LH concentration after regular methadone treatment for an average of 1 year (Zhang et al., 2014). However, other studies demonstrate that men receiving methadone for opioid abuse show decreased LH levels compared to controls without methadone (Hallinan et al., 2007; Woody et al., 1988). These differences in findings may be a result of differences in the doses of methadone used, as participants in Hallinan et al. (2007) and Woody et al. (1988) had higher mean daily doses of methadone. Similarly, methadone-naïve men show decreased LH levels following an acute exposure to methadone (Delitala et al., 1983). Male cancer survivors receiving opioids for chronic pain, including methadone, show decreased LH levels compared to controls (Rajagopal et al., 2004). In men illicitly using methadone, LH levels are not reduced from control levels (Azizi et al., 1973).

The research examining the effects of methadone on LH in women is

Table 1
Effects of methadone treatment for opiate dependence on hormone levels.

Outcome measure	Sex	Article	Experiment design	Sample size	Duration of treatment	Methadone dose	Hormone concentration	Results
Prolactin	Males	Brown et al., 2005	Hormone levels compared to standard ranges	92 methadone	3.3 years	100 mg	9.8 ± 6.7 ng/ml	No differences compared to standard ranges
		Cushman and Kreek, 1974	Hormone levels compared before and after methadone	8 methadone	3.4 ± 0.9 years	30 - 100 mg	8.1 ± 5.9 ng/ml	No differences after methadone
		Gerra et al., 2016	Hormone levels compared to controls	40 methadone, 40 controls	1 year	87.9 ± 26.6 mg	14.23 ± 6.5 ng/mL methadone group, 6.33 ± 3.80 ng/mL control group	Prolactin higher in methadone group compared to control group
		Hallinan et al., 2007	Hormone levels compared to controls	79 methadone, 79 controls	67 ± 58 months	106 ± 70 mg	6.9 ± 4.8 ng/L methadone group, 8.2 ± 2.7 ng/L control group	No differences compared to control group
		Hallinan et al., 2008	Hormone levels compared to standard ranges	84 methadone	67 ± 58 months	106 ± 70 mg	6.9 ± 4.7 ng/L	No differences compared to standard ranges
		Lafisca et al., 1981	Hormone levels compared to standard ranges	25 methadone	At least 2 months	30 mg	0.07–32.8 ng/mL	Prolactin higher in methadone group compared to standard ranges
		Ragni et al., 1988	Hormone levels compared to controls	23 methadone, 15 controls	14 ± 4 months	6 - 10 mg	6.7 ± 5.2 ng/ml methadone group, 5.9 ± 2.5 ng/ml control group	No differences compared to control group
		Spring et al., 1992	Hormone levels compared to standard ranges	25 methadone	32.9 ± 5.03 months	58.0 ± 1.81 mg	7.5 ± 5.7–7.8 ± 3.5 ng/ml	No differences compared to standard ranges
		Willenbring et al., 1989	Hormone levels compared to controls	15 methadone, 8 controls	18 months	52.7 mg	26.1 ± 3.7 ng/ml methadone group, 5.0 ± 0.4 ng/ml control group	Prolactin higher in methadone group compared to control group
		Woody et al., 1988	Hormone levels compared to controls	82 methadone, 16 controls	2 weeks - 2 or more years	0.9 ± 10 mg/kg	Not reported	Prolactin higher in methadone group compared to control group
		Trajanovska et al., 2013	Hormone levels compared to standard ranges	20 methadone	At least 3 years	60 - 120 mg	Not reported	No differences compared to standard ranges
	Females	Cofrancesco et al., 2006	Hormone levels compared to controls	33 methadone	Not reported	Not reported	7.33 ng/ml methadone group, 10.45 ng/ml control group	Prolactin lower in methadone group compared to control group
		Spagnolli et al., 1987	Hormone levels compared to controls	12 methadone, 33 controls	12 ± 3.7 days	15 - 35 mg	21.3 ± 2.6 ng/mL methadone group, 9.8 ± 0.7 ng/mL control group	Prolactin higher in methadone group compared to control group
Follicle-stimulating hormone (FSH)	Males	Bonakdaran et al., 2016	Hormone levels compared to controls	20 methadone, 40 controls	58.1 ± 28.6 months	59 ± 19.45 mg	4.02 ± 2.25 mIU/mL methadone group, 2.80 ± 1.49 mIU/mL control group	FSH higher in methadone group compared to control group
		Cushman and Kreek, 1974	Hormone levels compared before and after methadone	8 methadone	3.4 ± 0.9 years	30 - 100 mg	8.8 ± 2.9 mIu/ml	No differences after methadone
		Hallinan et al., 2007	Hormone levels compared to controls	79 methadone, 79 controls	67 ± 58 months	106 ± 70 mg	3.9 ± 2.1 U/L methadone group, 3.9 ± 1.7 U/L control group	No differences compared to control group
		Lafisca et al., 1981	Hormone levels compared to standard ranges	25 methadone	At least 2 months	30 mg	1.8–12.39 mIU/mL	FSH lower compared to standard ranges
		Ragni et al., 1988	Hormone levels compared to controls	23 methadone, 15 controls	14 ± 4 months	6 - 10 mg	7.6 ± 3.3 mIU/ml methadone group, 6.6 ± 1.9 mIU/ml control group	No differences compared to control group
		Spring et al., 1992	Hormone levels compared to standard ranges	25 methadone	32.9 ± 5.03 months	58 ± 1.81 mg	11.3 ± 5.5–14.7 ± 15.3 uIU/ml	No differences compared to standard ranges
	Females	Bonakdaran et al., 2016	Hormone levels compared to controls	20 methadone, 40 controls	58.1 ± 28.6 months	59 ± 19.45 mg	27.82 ± 20.41 mIU/mL methadone group, 36.04 ± 41.33 mIU/mL control group	No differences compared to control group
Luteinizing hormone (LH)	Males	Bonakdaran et al., 2016	Hormone levels compared to controls	20 methadone, 40 controls	58.1 ± 28.6 months	59 ± 19.45 mg	3.52 ± 3.25 mIU/mL methadone group, 3.07 ± 0.97 mIU/mL control group	No differences compared to control group
		Cushman, 1972	Hormone levels compared to controls	27 methadone, 14 controls	Not reported	Not reported	13.8 ± 5.4 mIU/mL methadone group, 11.5 ± 3.7 mIU/mL control group	No differences compared to control group

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Table 1 (*continued*)

Outcome measure	Sex	Article	Experiment design	Sample size	Duration of treatment	Methadone dose	Hormone concentration	Results
		Cushman, 1973	Hormone levels compared to controls	54 methadone, 16 controls	22 ± 8 months	92 ± 25 mg	11.5 ± 5.0 mIU/mL methadone group, 9.4 ± 3.1 mIU/mL control group	No differences compared to control group
		Cushman and Kreek, 1974	Hormone levels compared before and after methadone	8 methadone	3.4 ± 0.9 years	30 - 100 mg	13.8 ± 3.8 mIu/ml	No differences after methadone
		Hallinan et al., 2007	Hormone levels compared to controls	79 methadone, 79 controls	67 ± 58 months	106 ± 70 mg	3.9 ± 2.1 U/L methadone group, 7.2 ± 3.1 U/L control group	LH lower in methadone group compared to control group
		Hallinan et al., 2008	Hormone levels compared to standard ranges	84 methadone	67 ± 58 months	106 ± 70 mg	4.3 ± 5.5 ng/L	No differences compared to standard ranges
		Lafisca et al., 1981	Hormone levels compared to standard ranges	25 methadone	At least 2 months	30 mg	4.4–42.4 mIU/mL	No differences compared to standard ranges
		Ragni et al., 1988	Hormone levels compared to controls	23 methadone, 15 controls	14 ± 4 months	6 - 10 mg	9.3 ± 4.6 mIU/ml methadone group, 8.1 ± 2.9 mIU/ml control group	No differences compared to control group
		Spring et al., 1992	Hormone levels compared to standard ranges	25 methadone	32.9 ± 5.03 months	58 ± 1.81 mg	17.7 ± 9.9–24.1 ± 12.9 uIU/ml	No differences compared to standard ranges
		Woody et al., 1988	Hormone levels compared to controls	82 methadone, 16 controls	2 weeks - 2 or more years	0.9 ± 10 mg/kg	Not reported	LH lower in methadone group compared to control group
		Zhang et al., 2014	Hormone levels compared before and after methadone	43 methadone	1 month - 1.5 years	50 mL - 160 m L	4.02 ± 3.72 ug/dl before methadone, 3.42 ± 2.48 ug/dl after methadone	No differences after methadone
	Females	Bonakdaran et al., 2016	Hormone levels compared to controls	20 methadone, 40 controls	58.1 ± 28.6 months	59 ± 19.45 mg	12.00 ± 10.08 mIU/mL methadone group, 12.16 ± 10.24 mIU/mL control group	No differences compared to control group
Testosterone	Males	Agha-Mohammadhasani et al., 2018	Hormone levels compared to controls	70 total, no report of number methadone	At least 1 year	Not reported	4.76 ± 2.03 ng/dl methadone group, 6.05 ± 2.45 ng/dl control group	Testosterone lower in methadone group compared to control group
		Amini Lari et al., 2012	Hormone levels compared to standard ranges	97 methadone	Not reported	Not reported	Not reported	Testosterone lower in methadone group compared to standard ranges
		Bawor et al., 2014	Hormone levels compared to controls	131 methadone, 287 controls	40.6 ± 38.7 months	90.2 ± 65.6 mg	100.10 ± 72.21 ng/dL methadone group, 414.74 ± 141.81 ng/dL control group	Testosterone lower in methadone group compared to control group
		Bonakdaran et al., 2016	Hormone levels compared to controls	20 methadone, 40 controls	58.1 ± 28.6 months	59 ± 19.45 mg	346.43 ± 268.28 mIU/mL methadone group, 360.15 ± 109.48 mIU/mL control group	No differences compared to control group
		Brown et al., 2005	Hormone levels compared to standard ranges	92 methadone	3.3 years	100 mg	4.6 ± 3.3 ng/ml	No differences compared to standard ranges
		Cicero et al., 1975	Hormone levels compared to controls	29 methadone, 43 controls	At least 3 months	66.9 ± 3.6 mg	367 ± 41 ng/100 mL methadone group, 640 ± 59 ng/100 mL control group	Testosterone lower in methadone group compared to control group
		Cushman and Kreek, 1974	Hormone levels compared before and after methadone	8 methadone	3.4 ± 0.9 years mean	30 - 100 mg	878 ± 333 ng/100 ml	No differences after methadone
		Cushman, 1973	Hormone levels compared to controls	54 methadone, 16 controls	22 ± 8 months	92 ± 25 mg	577 ± 284 ng/dl methadone group, 598 ± 246 ng/dl control group	No differences compared to control group
		Gerra et al., 2016	Hormone levels compared to controls	40 methadone	1 year	87.9 ± 26.6 mg	419.13 ± 117.08 ng/dl methadone group, 576.65 ± 184.61 ng/dl control group	Testosterone lower in methadone group compared to control group
		Hallinan et al., 2007	Hormone levels compared to controls	79 methadone, 79 controls	67 ± 58 months	106 ± 70 mg	11.4 ± 7.0 nM methadone group, 18.9 ± 6.1 nM control group	Testosterone lower in methadone group compared to control group

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Table 1 (*continued*)

Outcome measure	Sex	Article	Experiment design	Sample size	Duration of treatment	Methadone dose	Hormone concentration	Results
		Hallinan et al., 2008	Hormone levels compared to standard ranges	84 methadone	67 ± 58 months	106 ± 70 mg	11.6 ± 7.0 pM	Testosterone lower in methadone group compared to standard ranges
		Lafisca et al., 1981	Hormone levels compared to standard ranges	25 methadone	At least 2 months	30 mg	95 - 1489.4 ng/dL	No differences compared to standard ranges
		Mendelson et al., 1975a	Hormone levels compared before and after methadone	10 methadone	7 days	35 mg, 5 mg decrements/day	Not reported	Testosterone lower after methadone compared to before methadone
		Mendelson et al., 1975b	Hormone levels compared to controls	28 methadone, 16 controls	1 year	10 - 150 mg	409.1 ± 181.9 mg/100 mL - 687.5 ± 243.8 mg/100 mL	Testosterone lower in methadone group compared to control group
		Ragni et al., 1988	Hormone levels compared to controls	23 methadone, 15 controls	14 ± 4 months	6 - 10 mg	4.8 ± 1.5 ng/ml methadone group, 4.9 ± 1.1 ng/ml control group	No differences compared to control group
		Spring et al., 1992	Hormone levels compared to standard ranges	25 methadone	32.9 ± 5.03 months	58 ± 1.81 mg	558 ± 320 ng/dl - 570 ± 238 ng/dl	No differences compared to standard ranges
		Woody et al., 1988	Hormone levels compared to controls	82 methadone, 16 controls	2 weeks - 2 or more years	0.9 ± 10 mg/kg	Not reported	Testosterone lower in methadone group compared to control group
		Zhang et al., 2014	Hormone levels compared before and after methadone	43 methadone	1 month - 1.5 years	50 mL - 160 m L	343.49 ± 126.41 ug/dl before methadone, 284.53 ± 91.36 ug/dl after methadone	Testosterone lower after methadone compared to before methadone
	Females	Bawor et al., 2014	Hormone levels compared to controls	100 methadone, 496 controls	36.4 ± 45.6 months	83.3 ± 52.8 mg	36.61 ± 23.19 ng/dL methadone group, 25.93 ± 15.20 ng/dL control group	No differences compared to standard ranges
		Cofrancesco et al., 2006	Hormone levels compared to controls	33 methadone	Not reported	Not reported	29.66 ng/dl methadone group, 35.98 ng/dl control group	Testosterone lower in methadone group compared to control group
Estrogens	Males	Hallinan et al., 2007	Hormone levels compared to controls	79 methadone, 79 controls	67 ± 58 months	106 ± 70 mg	71.7 ± 51.8 pM methadone group, 148.4 ± 62.1 pM control group	Estradiol lower in methadone group compared to control group
		Hallinan et al., 2008	Hormone levels compared to standard ranges	84 methadone	67 ± 58 months	106 ± 70 mg	71.7 ± 51.3 pM methadone group, 148.4 ± 62.1 pM control group	No differences compared to standard ranges
		Lafisca et al., 1981	Hormone levels compared to standard ranges	25 methadone	At least 2 months	30 mg	12.0–48 pg/mL	No differences compared to standard ranges
	Females	Bonakdaran et al., 2016	Hormone levels compared to controls	20 methadone, 40 controls	58.1 ± 28.6 months	59 ± 19.45 mg	52.72 ± 72.97 mIU/mL methadone group, 96.35 ± 100.50 mIU/mL control group	No differences compared to control group
Progesterone	Males	Lafisca et al., 1981	Hormone levels compared to standard ranges	25 methadone	At least 2 months	30 mg	0.04 - 0.33 ng/mL	Progesterone lower in methadone group compared to standard ranges

Duration of treatment represented as mean ± SD or range of treatment duration unless otherwise noted.
Dose represented as mean ± SD or range of doses unless otherwise noted.
Hormone concentrations represented as mean ± SD or range of concentrations unless otherwise noted.

Table 2
Effects of methadone treatment for chronic pain on hormone levels.

Outcome measure	Sex	Article	Experiment design	Sample size	Duration of treatment	Methadone dose	Hormone concentration	Results
Prolactin	Females	Rolandi and Barreca, 1978	Hormone levels compared before and after methadone	8 methadone	Single administration	10 mg	14.88 ± 4.57 ng/mL before methadone, 65.12 ± 18.06 ng/mL after methadone	Prolactin higher after methadone compared to before methadone
Follicle-stimulating hormone (FSH)	Males	Rajagopal et al., 2004	Hormone levels compared to controls	20 opioids including methadone, 20 controls	At least 1 year	Not reported	0.7–28.6 mIU/mL opioid group, 1.8–23.6 mIU/mL control group	No differences compared to control group
	Females	Daniell, 2008	Hormone levels compared to controls	31 opioids including methadone, 42 controls	Not reported	97 mg	Not reported	No differences compared to control group in pre-menopausal women, FSH lower in opioid group compared to control group in post-menopausal women
Luteinizing hormone (LH)	Males	Rajagopal et al., 2004	Hormone levels compared to controls	20 opioids including methadone, 20 controls	At least 1 year	Not reported	0.5–6.9 mIU/mL opioids group, 1.9–9.9 mIU/mL control group	LH lower in opioid group compared to control group
	Females	Daniell, 2008	Hormone levels compared to controls	31 opioids including methadone, 42 controls	Not reported	97 mg	Not reported	LH lower in opioid group compared to control group
Testosterone	Males	Daniell, 2002a	Hormone levels compared to controls	24 opioids including methadone, 27 controls	< 1 year - > 10 years	20 - > 240 mg	172.1 ± 108.8–265.8 ± 191.9 ng/dL opioid group, 449.1 ± 181.1 ng/dL control group	Testosterone lower in opioid group compared to control group
		Daniell, 2002b	Hormone levels compared to controls	22 methadone, 11 controls	Not reported	10 - > 120 mg	117.8–268 ng/dl methadone group, 466.7 ng/dl control group	Testosterone lower in methadone group compared to control group
		Rajagopal et al., 2004	Hormone levels compared to controls	20 opioids including methadone, 20 controls	At least 1 year	Not reported	21 - 379 ng/dL opioids group, 171–978 ng/dL control group	Testosterone is lower in opioid group compared to control group
		Ray et al., 2017	Hormone levels compared to controls	120 opioids including methadone, 80 controls	Not reported	Not reported	Not reported	No differences compared to control group
	Females	Daniell, 2008	Hormone levels compared to controls	31 opioids including methadone, 42 controls	Not reported	97 mg	3.9 ± 2.3–4.0 ± 3.5 pg/mL opioid group, 5.8 ± 3.9–7.0 ± 2.4 pg/mL control group	Testosterone lower in opioid group compared to control group in pre- and post-menopausal women
Estrogens	Males	Daniell, 2002a	Hormone levels compared to controls	24 opioids including methadone, 27 controls	< 1 year - > 10 years	20 - > 240 mg	11.7 ± 6.3–18.7 ± 8.4 pg/mL opioid group, 32.0 ± 17.2 pg/mL control group	Estradiol lower in opioid group compared to control group
	Females	Daniell, 2008	Hormone levels compared to controls	31 opioids including methadone, 42 controls	Not reported	97 mg	63.2 ± 56.7 pg/mL opioid group, 132.3 ± 108.1 pg/mL control group	Estradiol lower in opioid group compared to control group in pre-menopausal women
		Ray et al., 2017	Hormone levels compared to controls	120 opioids including methadone, 80 controls	Not reported	Not reported	Not reported	No differences compared to control group

Duration of treatment represented as mean ± SD or range of treatment duration unless otherwise noted.
Dose represented as mean ± SD or range of doses unless otherwise noted.
Hormone concentrations represented as mean ± SD or range of concentrations unless otherwise noted.

Table 3
Effects of illicit methadone abuse and methadone in drug-naïve participants hormone levels.

Outcome measure	Sex	Article	Experiment design	Sample size	Duration of use	Methadone dose	Hormone concentration	Results
Prolactin	Males	Judd et al., 1982	Hormone levels compared before and after methadone, drug-naïve participants	9 methadone	Two acute administrations	10 mg	14.7 ± 11.0 ng/mL before methadone, 35.1 ± 33.1 ng/mL after methadone	Prolactin higher after methadone compared to before methadone
Follicle-stimulating hormone (FSH)	Males	Azizi et al., 1973	Hormone levels compared to controls, illicit use of methadone	6 methadone, 22 controls	Not reported	60 - 140 mg	120 ± 63 ng/mL methadone group, 85 ± 21 ng/mL control group	No differences compared to control group
		Delitala et al., 1983	Hormone levels compared before and after methadone, drug-naïve participants	6 methadone	Acute administration	10 mg	Not reported	No differences after methadone
Luteinizing hormone (LH)	Males	Azizi et al., 1973	Hormone levels compared to controls, illicit use of methadone	6 methadone, 22 controls	Not reported	60 - 140 mg	102 ± 52.1 ng/mL methadone group, 70 ± 36 ng/mL control group	No differences compared to control group
		Delitala et al., 1983	Hormone levels compared before and after methadone, drug-naïve participants	6 in methadone group, subjects served as their own controls	Acute administration	10 mg	Not reported	LH lower after methadone compared to before methadone
Testosterone	Males	Azizi et al., 1973	Hormone levels compared to controls, illicit use of methadone	6 methadone, 22 controls	Not reported	60 - 140 mg	3.41 ± 1.14 ng/mL methadone group, 7.00 ± 2.87 ng/mL control group	Testosterone lower in methadone group compared to control group
Estrogens	Males	Azizi et al., 1973	Hormone levels compared to controls, illicit use of methadone	6 methadone, 22 controls	Not reported	60 - 140 mg	19.1 ± 5.2 ng/mL methadone group, 27 ± 12.2 ng/mL control group	No differences compared to control group
	Females	Facchinetti et al., 1986	Hormone levels compared to controls, illicit use of methadone	25 pregnant methadone, 21 pregnant controls, 7 non-pregnant methadone, 6 non-pregnant controls	Second and third trimester (3-6 months)	10 - 30 mg	4.41 ± 0.82 ng/mL methadone group, 8.20 ± 1.07 ng/mL control group	Estriol lower in methadone compared to controls in third trimester pregnant women

Duration of treatment represented as mean ± SD or range of treatment duration unless otherwise noted.
Dose represented as mean ± SD or range of doses unless otherwise noted.
Hormone concentrations represented as mean ± SD or range of concentrations unless otherwise noted.

Table 4
Effects of methadone on hormone levels in animal models.

Outcome measure	Sex	Article	Experiment design	Sample size	Duration of use	Methadone dose	Hormone concentration	Results
Prolactin	Males	Bartolome and Kuhn, 1983	Hormone levels compared to controls in rats	6–8 methadone, 6–8 controls	Acute administration	2.5 mg/kg	56 ± 14 ng/mL methadone group, 15 ± 2 ng/mL control group	Prolactin higher in methadone group compared to control group
		Clemens and Sawyer, 1974	Hormone levels compared to controls in rats	9 methadone, 10 controls	Acute administration	15 mg/kg	51.9 ± 1.3 ng/mL methadone group, 21.6 ± 1.5 ng/mL control group	Prolactin higher in methadone group compared to control group
		Kuhn and Bartolome, 1983	Hormone levels compared to controls in rats	8–10 methadone, 8–10 controls	Acute administration	2.5 mg/kg	17 ± 3 ng/mL methadone neonatal rats, 3 ± 1 ng/mL control neonatal rats, 55 ± 6 ng/mL methadone adult rats, 22 ± 4 ng/mL control adult rats	Prolactin higher in methadone group compared to control group in postnatal and adult rats
		Kuhn and Bartolome, 1984	Hormone levels compared to controls in rats	10–12 methadone, 10–12 controls	20 days	2.5 - 5 mg/kg	Not reported	Prolactin higher in methadone group compared to control group
		Kuhn and Bartolome, 1985	Hormone levels compared to controls in rats	At least 15 methadone, at least 15 controls	20 days	Escalating dose starting at 2.5 mg/kg	8 ± 2 ng/mL methadone group, 13 ± 1 ng/mL control group	Prolactin lower in methadone group compared to control group
		Shaar and Clemens, 1980	Hormone levels compared to controls in rats	12 methadone, 6 controls	Acute administration	1.0 mg/kg	89.5 ± 3.2 ng/ml methadone group, 15.0 ± 3.2 control group	Prolactin higher in methadone group compared to control group
	Females	Bartolome and Kuhn, 1983	Hormone levels compared to controls in rats	6–8 methadone, 6–8 controls	Acute administration	2.5 mg/kg	182 ± 58 ng/mL methadone group, 16 ± 2 ng/mL control group	Prolactin higher in methadone group compared to control group
		Hein et al., 1991	Hormone levels compared to controls in Cynomolgus monkeys	3 methadone, 3 controls	164 days (length of gestation)	40 mg	Not reported	No differences compared to control group
		Kuhn and Bartolome, 1983	Hormone levels compared to controls in rats	8–10 methadone, 8–10 controls	Acute administration	2.5 mg/kg	17 ± 3 ng/mL methadone neonatal rats, 3 ± 1 ng/mL control neonatal rats, 55 ± 6 ng/mL methadone adult rats, 22 ± 4 ng/mL control adult rats	Prolactin higher in methadone group compared to control group in postnatal and adult rats
		Kuhn and Bartolome, 1984	Hormone levels compared to controls in rats	10–12 methadone, 10–12 controls	20 days	2.5 - 5 mg/kg	Not reported	Prolactin higher in methadone group compared to control group
Follicle-stimulating hormone (FSH)	Males	Ghowsi and Yousofvand, 2015	Hormone levels compared to controls in rats	7 methadone, 7 controls	14 days	Varying doses of methadone self-administration in drinking water	0.19 ± 0.01 mIU/mL methadone group, 0.20 ± 0.01 mIU/mL control group	No differences compared to control group
	Females	Bui et al., 1983a	Hormone levels compared to controls in mice	4–5 methadone, 4–5 controls	1 - 15 days	10 mg/kg	2.10 mIU/mL methadone group, 10.36 mIU/mL control group	FSH lower in methadone group compared to control group
Luteinizing hormone (LH)	Males	Kuhn and Bartolome, 1985	Hormone levels compared to controls in rats	At least 15 methadone, at least 15 controls	20 days	Escalating dose starting at 2.5 mg/kg	9 ± 1 ng/mL methadone group, 23 ± 2 ng/mL control group	LH lower in methadone group compared to control group
		Singh et al., 1982	Hormone levels compared to controls in rats	5 methadone, 5 controls	Acute exposure	10 mg/kg	Not reported	LH lower in methadone group compared to control group
		Ghowsi and Yousofvand, 2015	Hormone levels compared to controls in rats	7 methadone, 7 controls	14 days	Varying doses of methadone self-administration in drinking water	1.10 ± 0.11 mIU/mL methadone group, 1.49 ± 0.28 mIU/mL control group	No differences compared to control group
	Females	Johnson and Rosecrans, 1978	Hormone levels compared to controls in rats	At least 25 methadone, at least 25 controls	Acute exposure	15 mg/kg	Not reported	LH lower in methadone group compared to control group

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Table 4 (*continued*)

Outcome measure	Sex	Article	Experiment design	Sample size	Duration of use	Methadone dose	Hormone concentration	Results
		Johnson and Rosecrans, 1980	Ovulation compared to controls in rats	45 methadone, 5 controls	Acute exposure	9 or 15 mg/kg	Not reported	Methadone blocked ovulation compared to control group, effect reversed with exogenous LH administration
Testosterone	Males	Cicero et al., 1976	Hormone levels compared to controls in rats	8-9 methadone, 10 vehicle controls	20 days	10 - 20 mg/kg	1.4 ± 0.3 ng/mL methadone group, 5.1 ± 0.8 ng/mL control group	Testosterone lower in methadone group compared to control group
		Ghowsi and Yousofvand, 2015	Hormone levels compared to controls in rats	7 methadone, 7 controls	14 days	Varying doses of methadone self-administration in drinking water	2.70 ± 0.87 ng/mL methadone group, 5.04 ± 1.01 control group	No differences compared to control group
		Jakubovic and McGeer, 1979	Hormone levels compared to controls in rat testicular cell culture	3-4 testicular cell cultures methadone group, 7 testicular cell cultures controls	Acute exposure	1 mM added to the cell culture	62 ± 5 % of control levels methadone group, 312 ± 21 ng/g testes weight control group	Testosterone lower in methadone group compared to control group
		Kuhn and Bartolome, 1985	Hormone levels compared to controls in rats	At least 15 methadone, at least 15 controls	20 days	Escalating dose starting at 2.5 mg/kg	0.6 ± 0.1 ng/mL methadone group, 2.8 ± 0.2 ng/mL control group	Testosterone lower in methadone group compared to control group
		Purohit et al., 1979	Hormone levels compared to controls in rats	7 methadone, 7 controls	10 days	10 mg/kg	474 ± 58 pg/mL methadone group, 2794 ± 393 pg/mL control group	Testosterone lower in methadone group compared to control group
		Singh et al., 1982	Hormone levels compared to controls in rats	5 methadone, 5 controls	Acute exposure	10 mg/kg	Not reported	Testosterone lower in methadone group compared to control group
		Soyka et al., 1978	Testes weights compared to controls in rats	8 methadone, 4 controls	136 days	Up to 20 mg/kg	0.88 ± 0.02 % body weight for testes methadone group, 0.68 ± 0.05 % body weight for testes control group	Testes higher in weight in methadone group compared to control group
		Thomas and Dombrosky, 1975	Testes weights compared to controls in mice	At least 6 methadone, at least 6 controls	10 days	5, 10 or 20 mg/kg	227.0 ± 6.1–229.2 ± 11.2 mg methadone groups, 271.8 ± 11.5 mg control group	Testes lower in weight in methadone group compared to control group
Estrogens	Females	Bui et al., 1983a	Hormone levels compared to controls in mice	4–5 methadone, 4–5 controls	1 - 15 days	10 mg/kg	74.9 ng/mL methadone group, 109.1 ng/mL control group	Estriol lower in methadone group compared to control group
		Bui et al., 1983b	Hormone levels compared to controls in rats	9 methadone, 8 controls	9 days	5 mg/kg	Not reported	Estriol lower in methadone group compared to control group on day 9 of gestation
		Hein et al., 1991	Hormone levels compared to controls in Cynomolgus monkeys	3 methadone, 3 controls	164 days (length of gestation)	40 mg	Not reported	No differences compared to control group
		Sheridan, 1978	Estrous cycle and estradiol uptake compared to controls in rats	5 methadone, 5 controls	10 days	10 mg/kg	67.0 ± 5.6 number silver grains per nucleur uptake methadone group, 67.8 ± 4.4 number silver grains per nucleur uptake control group	No difference in estrous cycle or adrenal and ovarian weights in adult rats in methadone group compared to vehicle controls
Progesterone	Females	Hein et al., 1991	Hormone levels compared to controls in Cynomolgus monkeys	3 methadone, 3 controls	164 days (length of gestation)	40 mg	Not reported	No differences compared to control group

Hormone concentrations represented as mean ± SD or range of concentrations unless otherwise noted.

limited. To the best of our knowledge, only one experimental study examined the effects of methadone on LH levels in women compared to drug-free controls. This study found that in pre- and post-menopausal women on methadone treatment for opioid abuse, methadone does not alter LH levels compared to controls without methadone (Bonakdaran et al., 2016). Although not specific to methadone only, Daniell (2008) showed that both pre- and post-menopausal women receiving opiate drug treatment for pain management, including methadone, have lower levels of LH compared to control pre- and post-menopausal women, with more pronounced effects in post-menopausal women (Daniell, 2008).

Chronic exposure to methadone (either 5 mg/kg/day for 20 days or 10 mg/kg/day with 1 mg/day incremental increases for 20 days) in young adult male rats decreases LH on days 10 and 20 compared to vehicle controls (Kuhn and Bartolome, 1985). Adult male rats acutely injected with methadone directly into the ventromedial hypothalamus show decreases in LH release compared to vehicle controls (Singh et al., 1982). LH levels are not altered in adult male rats chronically exposed to varying doses of methadone in drinking water for 14 days compared to vehicle controls (Ghowsi and Yousofvand, 2015).

In female adult rats, acute methadone exposure (15 mg/kg) blocks the release of LH normally occurring in the late proestrus phase of the cycle and results in less frequent ovulatory phases than in female rats treated with vehicle or untreated controls (Johnson and Rosecrans, 1978). Acute methadone exposure (9 mg/kg and 15 mg/kg) prevents ovulation entirely in female adult rats compared to vehicle controls, although this effects was mitigated with exogenous LH administration (Johnson and Rosecrans, 1980).

3.5. Testosterone

In men receiving methadone for opioid abuse, total plasma testosterone levels are reduced from control levels (Agha-Mohammadhasani et al., 2018; Bawor et al., 2014; Cicero et al., 1975; Gerra et al., 2016; Hallinan et al., 2007; Mendelson et al., 1975b; Woody et al., 1988) and compared to standard ranges (Hallinan et al., 2008). Testosterone levels are lower in men after receiving methadone compared to before methadone treatment (Mendelson et al., 1975a). Other studies, however, show no differences in total plasma testosterone levels in men receiving methadone treatment for opioid abuse compared to standard ranges (Brown et al., 2005; Lafisca et al., 1981; Spring et al., 1992) or compared to controls (Bonakdaran et al., 2016; Cushman, 1973; Ragni et al., 1988). In addition, men receiving methadone for treatment of opiate abuse do not show any acute changes in testosterone concentration before or after their regularly scheduled doses of methadone (Cushman and Kreek, 1974), although there is a reduction in plasma testosterone levels in men after an average of 1 year on methadone treatment (Zhang et al., 2014). In men receiving methadone for pain management, plasma total testosterone levels are reduced from control levels (Daniell, 2002a, 2002b; Rajagopal et al., 2004). HIV-infected men on methadone for opiate abuse also demonstrate lowered total free serum testosterone levels compared to standard ranges (Amini Lari et al., 2012). In contrast, Ray et al. (2017) found that samples of serum from men receiving opiates, including methadone, for pain management do not have altered serum free testosterone levels compared to controls without opiates (Ray et al., 2017). Azizi et al. (1973) show that men illicitly using methadone have decreased total serum testosterone concentrations compared to controls (Azizi et al., 1973).

Few studies have examined the effects of methadone on testosterone levels in women. Methadone treatment for opiate abuse has no effect on serum total testosterone levels in women compared to standard ranges (Bawor et al., 2014). In contrast, HIV-infected women on methadone for opiate abuse show lower serum total testosterone levels compared to controls (Cofrancesco et al., 2006) and pre- and post-menopausal women receiving sustained-action opioids, including methadone, for treatment of chronic pain have significantly lower average total and free plasma testosterone levels compared to pre- and post-menopausal controls not consuming opioids (Daniell, 2008).

Acute injection of methadone (10 mg/kg) directly into the ventromedial hypothalamus in adult male rats decreases testosterone levels compared to vehicle controls at 15, 30, and 60 min post-exposure (Singh et al., 1982). In young adult male rats, chronic exposure to methadone (5 mg/kg/day for 20 days) does not attenuate serum testosterone, whereas higher doses of methadone (5 mg/kg twice per day, increasing 1 mg/kg/day for 20 days) decrease serum testosterone levels compared to vehicle controls on days 5, 10, and 20 (Kuhn and Bartolome, 1985). Chronic methadone exposure (5 mg/kg/day or 7.5 mg/kg/twice per day for 5 days and 10 mg/kg/day for 10 days) reduces testosterone levels, seminal vesicles weight, and prostrate weight in male rats on days 10 and 20 (Cicero et al., 1976). Purohit and colleagues (1979) also demonstrate that chronic exposure to methadone (10 mg/kg/day for 10 days) decreases testosterone levels, seminal vesicle weight, and prostrate weight in adolescent male rats compared to vehicle controls (Purohit et al., 1979). Daily injections of methadone (5 mg/kg, 10 mg/kg, or 20 mg/kg) for 10 days results in a dose-dependent reduction in prostrate weight, seminal vesicle weight, and testicular weight in adult male mice compared to vehicle controls (Thomas and Dombrosky, 1975). On the other hand, Soyka and colleagues (1978) find that methadone increases testicular weight, but does not affect seminal vesicle weight or prostrate weight, in adult male rats compared to controls (Soyka et al., 1978). Testosterone levels and teste, prostate, and seminal vesicle weight are not altered in adult male rats chronically exposed to varying doses of methadone in drinking water for 14 days compared to vehicle controls (Ghowsi and Yousofvand, 2015).

Methadone reduces *in vitro* testosterone production in rat testicular cell cultures compared to saline control (Jakubovic and McGeer, 1979).

3.6. Estrogens

Few studies have examined the effects of methadone on estrogens in men or women. Estradiol levels are reduced in men using methadone for opiate abuse treatment compared to controls (Hallinan et al., 2007). Estradiol levels are not changed from standard reference range levels in men receiving methadone for opioid abuse (Hallinan et al., 2008; Lafisca et al., 1981) or in men illicitly using methadone compared to controls (Azizi et al., 1973). Men receiving sustained-action opioids, including methadone, for pain management exhibit decreased estradiol levels compared to controls (Daniell, 2002a).

Compared to controls, methadone has no effect on estradiol levels in women receiving methadone treatment for opioid abuse (Bonakdaran et al., 2016). Serum samples from women using opiates, including methadone, for pain management show no changes in estradiol levels compared to samples from controls not using opiates (Ray et al., 2017). In contrast, estradiol levels decrease in pre-menopausal women receiving sustained-action opioids, including methadone, for chronic pain compared to pre-menopausal controls without methadone (Daniell, 2008). Pregnant women illicitly using methadone show depressed estriol levels in the third trimester compared to pregnant drug-naïve controls (Facchinetti et al., 1986).

Chronic administration of methadone (40 mg/day for 160 days) in pregnant monkeys does not change serum estradiol levels compared to controls (Hein et al., 1991). Moreover, chronic administration of methadone (10 mg/day for 10 days) in adult female rats has no effect on the estrous cycle, nor any effect of ^{3}H-estradiol nuclear uptake in the central nervous system following administration of estradiol (Sheridan, 1978). Chronic administration of methadone (10 mg/kg/day for 15 days) reduces estriol in pregnant mice by gestation day 15 (Bui et al., 1983a). Similarly, 5 mg/kg/day methadone inhibits plasma estriol in pregnant rats on day 9 of gestation (Bui et al., 1983b).

Table 5
Effects of methadone on sexual function.

Reason for methadone use	Sex	Article	Experiment design	Sample size	Duration of treatment	Methadone dose	Results
Methadone treatment for opiate dependence	Males	Agha-Mohammadhasani et al., 2018	Sexual function compared to controls	70 total, no report of number methadone	At least 1 year	Not reported	Lower erectile function, orgasmic function, sexual desire, and intercourse satisfaction in methadone group compared to control group, dose of methadone correlated with sexual dysfunction
		Amini Lari et al., 2012	Sexual function examined in methadone group	97 methadone	Not reported	Not reported	Impaired sexual desire, erectile function, and ejaculatory function
		Babakhanian et al., 2012	Sexual function compared before and after methadone	30 methadone	6 months	10.9–31.28 mg	Improvement of erectile dysfunction, sexual desire, and intercourse satisfaction after 6 months on methadone
		Briand Madrid et al., 2018	Sexual function examined in methadone group	29 methadone	Not reported	Not reported	Impaired libido
		Brown et al., 2005	Sexual function compared to standard ranges	92 methadone	3.3 years (mean)	100 mg	No differences compared to standard ranges, dose of methadone correlated with organism dysfunction
		Chekuri et al., 2012	Sexual function examined in methadone group	65 methadone	Not reported	71.95 ± 26.45 mg	Impaired erectile function, orgasmic function, sexual desire, intercourse satisfaction, and increased premature ejaculation
		Cheng et al., 2017	Sexual function examined in methadone group	187 methadone	54 ± 26.25 months	58.99 ± 34.71 mg	Impaired erectile function, methadone dose correlated with severity of erectile dysfunction
		Cicero et al., 1975	Sexual function compared to controls	29 methadone, 43 controls	At least 3 months	66.9 ± 3.6 mg	Impaired erectile function and delayed ejaculation in methadone group compared to control group
		Cushman, 1972	Sexual function compared to controls	27 methadone, 14 controls	Not reported	Not reported	Impaired erectile function and delayed ejaculation in methadone group compared to control group
		Cushman, 1973	Sexual function compared before and after methadone	54 methadone	1 year	92 ± 25 mg	Improvement of erectile dysfunction and sexual desire after 1 year on methadone
		Gerra et al., 2016	Sexual function compared to controls	40 methadone, 40 controls	1 year	87.9 ± 26.6 mg	Impaired orgasm function and sexual desire in methadone group compared to control group
		Gronbladh and Ohlund, 2011	Sexual function compared before and after methadone	72 methadone	Not reported	Not reported	Impaired erectile function, libido, and reaching sexual climax after 1 year on methadone
		Hallinan et al., 2008	Sexual function compared to reference group	53 methadone	67 ± 58 months	106 ± 70 mg	Impaired in methadone group compared to reference group
		Hanbury et al., 1977	Sexual function examined in methadone group	50 methadone	24.06 months	62.4 mg	Impaired sexual desire, erectile function, delayed ejaculation, and reaching sexual climax
		Hosseini et al., 2013	Sexual function examined in methadone group	200 methadone	Not reported	Not reported	Impaired erectile function, intercourse satisfaction, orgasm function, and sexual desire
		Kheradmand et al., 2015	Sexual function examined in methadone group	198 methadone	At least 6 months	Not reported	Impaired sexual function score
		Llanes et al., 2019	Sexual function examined in methadone group	77 methadone	6.34 ± 6.74 years	45.33 ± 25.29 mg	Impaired erectile function, reaching climax, and sexual desire, methadone dose correlated with sexual dysfunction
		Lugoboni et al., 2017	Sexual function examined in methadone group	598 methadone	Not reported	58.0 ± 47.3 mg	Impaired erectile function
		Nik Jaafar et al., 2013	Sexual function examined in methadone group	108 methadone	24.36 ± 6.33 months	62.50 ± 17.06 mg	Impaired erectile function
		Novick et al., 1993	Sexual function examined in methadone group	111 methadone	14.5 ± 0.1 years	60.2 ± 3.1 mg	Impaired erectile function, no effect on libido or ejaculations
		Parvaresh et al., 2015	Sexual function compared before and after methadone	180 methadone	6 months	30 - 140 mg	Impaired sexual function after 6 months on methadone
		Quaglio et al., 2008	Sexual function examined in methadone group	85 methadone	1 - 47 months	10 - 180 mg	Impaired erectile function
		Rajabizadeh et al., 2017	Sexual function examined in methadone group	Not reported	At least 8 weeks	33.28 ± 24.82 mg	Impaired sexual function
		Ragni et al., 1985	Semen examined in methadone group	7 methadone	18.5 months	40 - 60 mg	Impaired sperm count and sperm motility
		Ragni et al., 1988	Semen examined in methadone group	22 methadone	14 ± 4 months	6 - 10 mg	Impaired ejaculate volume, sperm motility, and increased infertile sperm

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Table 5 (*continued*)

Reason for methadone use	Sex	Article	Experiment design	Sample size	Duration of treatment	Methadone dose	Results
		Spring et al., 1992	Sexual function compared to standard ranges	25 methadone	32.9 ± 5.03 months	58.0 ± 1.81 mg	No differences compared to standard ranges, dose of methadone correlated with sexual dysfunction
		Teoh et al., 2017	Sexual function examined in methadone group	134 methadone	48.8 ± 32.8 months	72.1 ± 32.6 mg	Impaired erectile function
		Trajanovska et al., 2013	Sexual function examined in methadone group	20 methadone	At least 3 years	60 - 120 mg	Impaired erectile function, orgasm function, and libido
		Xia et al., 2013	Sexual function examined in methadone group	13 methadone	Not reported	Not reported	Impaired libido and intercourse satisfaction
		Zhang et al., 2011	Sexual function compared before and after methadone	612 methadone	195.4 ± 27.3 days	68.3 ± 8.1 mg	Impairment of erectile function and sexual desire after methadone, dose of methadone correlated with sexual dysfunction
		Zhang et al., 2014	Sexual function compared before and after methadone	293 methadone	1 month - 1.5 years	50 mL - 160 m L	Impairment of erectile function, sexual desire, orgasm function, and intercourse satisfaction after methadone
	Females	Briand Madrid et al., 2018	Percentage of methadone users showing sexual dysfunction	29 methadone	Not reported	Not reported	Loss of libido
		Gronbladh and Ohlund, 2011	Sexual function compared before and after methadone	31 on methadone	Not reported	Not reported	Impaired menstrual function, libido, and reaching sexual climax after 1 year on methadone
		Haber et al., 2017	Menstrual function examined in methadone group	184 methadone	4 years	85 mg	Impaired menstrual function
		Llanes et al., 2019	Sexual function examined in methadone group	13 methadone	9.85 ± 7.78 years	69.38 ± 43.92 mg	Impaired libido, ability to reach climax, and lubrication ability, methadone dose correlated with degree of dysfunction
		Parvaresh et al., 2015	Sexual function compared before and after methadone	19 methadone	6 months	30 - 140 mg	Impaired sexual function after 6 months on methadone
		Xia et al., 2013	Sexual function examined in methadone group	14 on methadone	Not reported	Not reported	Impaired libido and orgasm function
Methadone treatment for chronic pain	Males	Rajagopal et al., 2004	Sexual function compared to controls	20 opioids including methadone, 20 controls	At least 1 year	Not reported	Lower sexual function in methadone group compared to control group
		Daniell, 2002a	Sexual function examined in methadone group	24 opioids including methadone, 27 controls	< 1 year - > 10 years	20 - > 240 mg	Impaired erectile function
Methadone administration in animal models	Males	Murphy, 1981	Sexual function compared before and after methadone in hamsters	10 methadone	Acute exposure	1 - 16 mg/kg	Impaired copulatory intromissions and mounting after methadone

Duration of treatment represented as mean ± SD or range of treatment duration unless otherwise noted.
Dose represented as mean ± SD or range of doses unless otherwise noted.

3.7. Progesterone

Men receiving methadone treatment for opioid abuse exhibit decreased progesterone levels compared to standard reference ranges (Lafisca et al., 1981). To the best of our knowledge there are no studies that examine the effects of methadone on progesterone levels in women. Chronic administration of methadone (10 mg/kg/day for 160 days) does not alter serum progesterone in pregnant monkeys compared to vehicle controls (Hein et al., 1991).

3.8. Sexual function

Methadone's effects on the HPG axis and hormone levels can result in alterations in sexual behavior and function (Table 5). Various aspects of sexual behavior and function are impaired by methadone in men. Men treated with methadone for opioid abuse self-report an increase in sexual dysfunction following initiation of treatment (Amini Lari et al., 2012; Kheradmand et al., 2015; Llanes et al., 2019; Parvaresh et al., 2015; Rajabizadeh et al., 2017; Zhang et al., 2011), although sexual dysfunction can improve over time with continual methadone treatment (Babakhanian et al., 2012). Numerous studies report that men treated with methadone for opioid abuse have some degree of erectile dysfunction (Agha-Mohammadhasani et al., 2018; Amini Lari et al., 2012; Chekuri et al., 2012; Cheng et al., 2017; Cicero et al., 1975; Cushman, 1972; Gronbladh and Ohlund, 2011; Hallinan et al., 2008; Hanbury et al., 1977; Hosseini et al., 2013; Llanes et al., 2019; Lugoboni et al., 2017; Nik Jaafar et al., 2013; Novick et al., 1993; Quaglio et al., 2008; Teoh et al., 2017; Trajanovska et al., 2013; Zhang et al., 2014), orgasmic dysfunction (Agha-Mohammadhasani et al., 2018; Chekuri et al., 2012; Cushman, 1972; Gerra et al., 2016; Gronbladh and Ohlund, 2011; Hanbury et al., 1977; Llanes et al., 2019; Trajanovska et al., 2013; Zhang et al., 2011, 2014), decreased libido (Agha-Mohammadhasani et al., 2018; Amini Lari et al., 2012; Briand Madrid et al., 2018; Chekuri et al., 2012; Gerra et al., 2016; Hanbury et al., 1977; Hosseini et al., 2013; Llanes et al., 2019; Trajanovska et al., 2013; Xia et al., 2013; Zhang et al., 2011, 2014), and lack of intercourse satisfaction (Agha-Mohammadhasani et al., 2018; Chekuri et al., 2012; Hanbury et al., 1977; Hosseini et al., 2013; Trajanovska et al., 2013; Xia et al., 2013; Zhang et al., 2014) compared to controls. Similarly, men receiving long-acting opioids, including methadone, for chronic pain have increased sexual dysfunction compared to controls without opioids (Rajagopal et al., 2004) and men receiving opiates, including methadone, for pain show high rates of erectile dysfunction (Daniell, 2002a). While some studies show that methadone dose is not associated with sexual dysfunction (Chekuri et al., 2012; Gerra et al., 2016; Nik Jaafar et al., 2013; Zhang et al., 2014), other studies demonstrate a significant correlation between methadone dose and sexual dysfunction (Agha-Mohammadhasani et al., 2018; Brown et al., 2005; Spring et al., 1992; Zhang et al., 2011). There are few studies that show no effect of methadone on sexual behavior or function in men. For example, men treated with methadone for opioid abuse for 11–18 years self-report having normal libidos and normal ejaculations (Novick et al., 1993). Cushman (1973) found that compared to self-reported baseline measurements prior to treatment, men treated with methadone for opioid abuse show no differences in libido, erectile function, or ejaculation time after starting methadone treatment (Cushman, 1973).

Opioid-abusing men therapeutically treated with methadone have decreased ejaculate volume and decreased sperm motility (Cicero et al., 1975; Ragni et al., 1988, 1985), as well as higher levels of infertile sperm (Ragni et al., 1988) compared to controls without methadone. In contrast, Cicero et al. (1975) found sperm count of men on methadone to be similar to that of controls with less than 2 days of sexual abstinence. However, for periods of sexual abstinence greater than 3 days, sperm counts were significantly greater in methadone-treated men than those of controls (Cicero et al., 1975).

Studies examining the effects of methadone treatment on sexual function in women are limited. Women maintained on methadone for opioid abuse report sexual dysfunction (Parvaresh et al., 2015) and menstrual problems (Gronbladh and Ohlund, 2011; Haber et al., 2017). Women treated with methadone for opiate abuse self-report a decrease in libido (Briand Madrid et al., 2018; Llanes et al., 2019; Xia et al., 2013), delayed or inhibited orgasm (Llanes et al., 2019; Xia et al., 2013), and lubrication difficulty (Llanes et al., 2019). People treated with methadone for opiate abuse, including women, demonstrate decreases in libido and difficulty reaching orgasm (Gronbladh and Ohlund, 2011).

Studies examining the effects of methadone on sexual function in animal models are also limited. In adult male hamsters, acute exposure to methadone (8 mg/kg) reduces copulatory intromissions and mounting behavior and a higher dose of methadone (16 mg/kg) eliminates copulatory intromissions (Murphy, 1981). These effects of methadone on sexual function and behaviors are not observed at lower doses of methadone (Murphy, 1981).

4. Discussion

This systematic review examined the literature assessing the effect of methadone on the HPG axis, hormone levels, and sexual function in males and females. To the best of our knowledge, this is the first systematic review to examine the specific effects of methadone on the HPG axis and sexual function in both males and females. While hypogonadism and sexual dysfunction are common side effects with methadone treatment, our review of the literature suggests that the relationship between methadone and hormone levels and sexual function is complex and may vary depending on age, sex, dose, and length of methadone exposure.

There is evidence that methadone affects hormone levels and HPG axis function via either hypothalamic and/or pituitary inhibition or direct action on the secondary sex organs and gonads. The μ-opiate receptors are expressed in the hypothalamus (Bedos et al., 2019; Katz and Mazer, 2009; Le Merrer et al., 2009), the pituitary gland (Carretero et al., 2004; Katz and Mazer, 2009), the testes (Estomba et al., 2016; Wittert et al., 1996) and the ovaries (Kaminski, 2006; Wittert et al., 1996). Under typical conditions, low levels of testosterone or estradiol signal the hypothalamus to release more GnRH, which subsequently stimulates the production of FSH and LH in the anterior pituitary, resulting in increased sperm production and testosterone by the testes in males and increased estradiol and progesterone in females (Colameco and Coren, 2009; Smith and Elliott, 2012). Based on this review, there appears to be ample evidence to suggest that methadone has inhibitory action on the hypothalamus and GnRH, thus reducing hormone secretion from the anterior pituitary and the production of sex hormones.

Elevated levels of prolactin inhibit the pulsatile secretion of GnRH from the hypothalamus and consequently inhibit the release of FSH and LH. This can result in a decrease in testosterone and estradiol (for a review, see (Dabbous and Atkin, 2018; Grattan, 2015)). While some of the reviewed studies suggest that methadone treatment does not alter prolactin levels (Brown et al., 2005; Cushman and Kreek, 1974; Hallinan et al., 2008, 2007; Hein et al., 1991; Ragni et al., 1988; Spring et al., 1992; Trajanovska et al., 2013), the majority of studies show that methadone does indeed increase prolactin levels, suggesting that one mechanism by which methadone can disrupt the HPG axis is by increasing prolactin levels and subsequently decreasing pulsatile release of GnRH from the hypothalamus (Bartolome and Kuhn, 1983; Clemens and Sawyer, 1974; Gerra et al., 2016; Judd et al., 1982; Kuhn and Bartolome, 1984, 1983; Lafisca et al., 1981; Rolandi and Barreca, 1978; Shaar and Clemens, 1980; Spagnolli et al., 1987; Willenbring et al., 1989; Woody et al., 1988). Elevated levels of prolactin are also associated with erectile dysfunction in men (De Rosa et al., 2004), suggesting methadone's effects on prolactin levels could be one mechanism by which methadone causes sexual dysfunction.

The majority of the studies reviewed show no effect of methadone

on FSH levels in males or females (Azizi et al., 1973; Bonakdaran et al., 2016; Cushman and Kreek, 1974; Delitala et al., 1983; Ghowsi and Yousofvand, 2015; Hallinan et al., 2007; Ragni et al., 1988; Rajagopal et al., 2004; Spring et al., 1992). Only 2 studies in humans that were reviewed show methadone decreases FSH levels, but these studies were confounded by concurrent drug use (Lafisca et al., 1981) and treatment with other opiates in addition to methadone (Daniell, 2008). One study found increased FSH levels compared to controls in men using methadone for opiate abuse treatment, but this effect was not related to methadone dose or duration or use (Bonakdaran et al., 2016). The effects of methadone on LH levels were less consistent among the studies reviewed. The majority of studies show that methadone does not alter LH levels (Azizi et al., 1973; Bonakdaran et al., 2016; Cushman, 1972, 1973; Cushman and Kreek, 1974; Ghowsi and Yousofvand, 2015; Hallinan et al., 2008; Lafisca et al., 1981; Ragni et al., 1988; Spring et al., 1992; Zhang et al., 2014), while some studies show that methadone decreases LH levels (Daniell, 2008; Delitala et al., 1983; Hallinan et al., 2007; Johnson and Rosecrans, 1978; Kuhn and Bartolome, 1985; Rajagopal et al., 2004; Singh et al., 1982; Woody et al., 1988). The differences in these findings may be due to a variety of factors, including vast differences in dosing regimens, time of hormone measurement, and duration of methadone exposure. A decrease in both LH and FSH levels with methadone could be explained by an increase in prolactin levels with methadone (De Rosa et al., 2004) and the decrease in GnRH release from the hypothalamus with methadone treatment. However, the lack of changes in FSH and LH levels found in the majority of the methadone-treated participants may be due to lower sex hormone levels and thus a lack of negative feedback inhibition on FSH and LH release (Plant, 2015; Shaw et al., 2010). Alternatively, the lack of an effect of methadone on FSH and LH levels may be due to methadone exerting much of its effects at the level of the secondary sex organs and the gonads (discussed further below).

The majority of the reviewed studies found that methadone decreases testosterone levels (Agha-Mohammadhasani et al., 2018; Amini Lari et al., 2012; Azizi et al., 1973; Bawor et al., 2014; Cicero et al., 1975, 1976; Cofrancesco et al., 2006; Daniell, 2002a, 2002b, 2008; Gerra et al., 2016; Hallinan et al., 2008, 2007; Jakubovic and McGeer, 1979; Kuhn and Bartolome, 1985; Mendelson et al., 1975a, b; Purohit et al., 1979; Rajagopal et al., 2004; Singh et al., 1982; Woody et al., 1988; Zhang et al., 2014). Injection of methadone directly into the hypothalamus decreases testosterone in male rats, suggesting one mechanism by which methadone decreases testosterone is via inhibition of GnRH release from the hypothalamus and disruption of the HPG axis (Singh et al., 1982). However, fewer of the reviewed studies found no effect of methadone treatment on testosterone levels (Bawor et al., 2014; Bonakdaran et al., 2016; Brown et al., 2005; Cushman, 1973; Cushman and Kreek, 1974; Ghowsi and Yousofvand, 2015; Lafisca et al., 1981; Ragni et al., 1988; Ray et al., 2017; Spring et al., 1992). The discrepancy in results could be due in part to lower doses of methadone used in the studies that did not find an effect of methadone on testosterone levels and a higher average age of the participants in some of these studies. A recent meta-analysis review of the effects of opiates, including methadone, on testosterone levels found opiates reduce testosterone levels in men but not in women (Bawor et al., 2015). The majority of studies reviewed found estrogen levels are not altered by methadone treatment (Azizi et al., 1973; Bonakdaran et al., 2016; Hallinan et al., 2008; Hein et al., 1991; Lafisca et al., 1981; Ray et al., 2017) and progesterone levels are not altered by methadone in pregnant monkeys (Hein et al., 1991), although there are no studies examining the effects of methadone on progesterone in women. However, some studies found methadone does decrease estrogen levels (Daniell, 2002a, 2008; Hallinan et al., 2007), including reductions in estriol levels in pregnant women (Facchinetti et al., 1986), pregnant mice (Bui et al., 1983a), and pregnant rats (Bui et al., 1983b). As noted above, the reductions in testosterone and estrogen levels with methadone treatment could be due to methadone's effects on the HPG axis and reductions in GnRH, LH, and FSH levels (Katz and Mazer, 2009). Alternatively, methadone may alter testosterone and estrogen levels via direct actions on the secondary sex organs and the gonads.

It has been hypothesized that methadone can exert its effects by directly acting on secondary sex organs and inhibiting the gonads from producing sex steroids. For example, methadone decreases ejaculate volume and sperm motility (Cicero et al., 1975; Ragni et al., 1988; Ragni et al., 1985). In male rodents, methadone reduces seminal vesicle weight (Cicero et al., 1976; Purohit et al., 1979; Thomas and Dombrosky, 1975), prostate weight (Cicero et al., 1976; Purohit et al., 1979; Thomas and Dombrosky, 1975), and testicular weight (Thomas and Dombrosky, 1975). Direct inhibition of the gonads and decreased production of testosterone and estrogens would result in a decrease in the negative feedback regulation of the hypothalamus and pituitary gland, thereby increasing FSH and LH levels (Katz and Mazer, 2009). Evidence for this mechanism of action can be seen in studies such as Hallinan et al. (2008) that report men receiving methadone have low testosterone levels, but LH concentrations are within normal ranges, suggesting a primary testicular pathology of hypogonadism (Hallinan et al., 2008).

Methadone's effects on the HPG axis and sex steroids alters sexual function. The majority of the studies reviewed show impairments in sexual function with methadone treatment (Agha-Mohammadhasani et al., 2018; Amini Lari et al., 2012; Briand Madrid et al., 2018; Chekuri et al., 2012; Cheng et al., 2017; Cicero et al., 1975; Cushman, 1972; Daniell, 2002a; Gerra et al., 2016; Gronbladh and Ohlund, 2011; Hallinan et al., 2008; Hanbury et al., 1977; Hosseini et al., 2013; Kheradmand et al., 2015; Llanes et al., 2019; Lugoboni et al., 2017; Murphy, 1981; Nik Jaafar et al., 2013; Novick et al., 1993; Parvaresh et al., 2015; Quaglio et al., 2008; Rajabizadeh et al., 2017; Rajagopal et al., 2004; Teoh et al., 2017; Trajanovska et al., 2013; Xia et al., 2013; Zhang et al., 2014, 2011). Only 2 studies reviewed show no effect of methadone on some aspects of sexual function (Cushman, 1973; Novick et al., 1993). Both of these studies are longitudinal studies examining participants 1 year after treatment initiation (Cushman, 1973) or after 11–18 years of methadone treatment (Novick et al., 1993). The longer duration of treatment may account for the lack of a self-reported effect of methadone on sexual function in these studies.

5. Conclusions

The majority of the research suggests that methadone impairs HPG axis function, resulting in hypogonadism and impairments in sexual function. There is also evidence for direct effects of methadone on secondary sex organs and the gonads, affecting sex steroid hormone levels. Considerations of HPG axis function, hypogonadism, and sexual function should be taken into account in the use of methadone as a treatment for opiate abuse or chronic pain. Despite the wealth of evidence suggesting methadone alters hormone levels and impairs sexual function, there are a large number of discrepancies in the literature reviewed, thus elucidating the limitations about the current knowledge of the effects of methadone on the HPG axis, sex hormones, and sexual function. There is discrepancy among the reviewed studies in sample size, presence of concurrent drug use, duration of methadone treatment, sexual function questionnaires, and time of day the blood was drawn in respect to last methadone dose. Very few studies examine the effects of methadone in women, limiting the generalizability of the findings. Future research is warranted to further examine the effects of methadone on the HPG axis and hormone levels, especially in females, to better understand the mechanisms by which methadone alters hormones and sexual function.

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References

Agha-Mohammadhasani, P., Mokhtaree, M., Nazari, A., Rahnama, A., 2018. Comparison of sexual function and serum testosterone levels in men opiate addicts, under methadone maintenance therapy, and healthy men. Addict. Health 10, 76–85.
Amini Lari, M., Parsa, N., Marzban, M., Shams, M., Faramarzi, H., 2012. Depression, testosterone concentration, sexual dysfunction and methadone use among men with hypogonadism and HIV Infection. AIDS Behav. 16, 2236–2243.
Azizi, F., Vagenakis, A.G., Longcope, C., Ingbar, S.H., Braverman, L.E., 1973. Decreased serum testosterone concentration in male heroin and methadone addicts. Steroids 22, 467–472.
Babakhanian, M., Alam Mehrjerdi, Z., Shenaiy, Y., 2012. Sexual dysfunction in male crystalline heroin dependents before and after MMT: a pilot study. Arch. Iran. Med. 15, 751–755.
Babakhanian, M., Haghdoost, A.A., Afshari, M., Taghizadeh, F., Moosazadeh, M., 2017. Methadone replacement therapy and sexual disorders among opium dependent iranian men: a meta-analysis study. Addict. Health 9, 1–10.
Bartolome, M.B., Kuhn, C.M., 1983. Endocrine effects of methadone in rats; acute effects in adults. Eur. J. Pharmacol. 95, 231–238.
Bawor, M., Bami, H., Dennis, B.B., Plater, C., Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Steiner, M., Anglin, R., Coote, M., Pare, G., Thabane, L., Samaan, Z., 2015. Testosterone suppression in opioid users: a systematic review and meta-analysis. Drug Alcohol Depend. 149, 1–9.
Bawor, M., Dennis, B.B., Samaan, M.C., Plater, C., Worster, A., Varenbut, M., Daiter, J., Marsh, D.C., Desai, D., Steiner, M., Anglin, R., Coote, M., Pare, G., Thabane, L., Samaan, Z., 2014. Methadone induces testosterone suppression in patients with opioid addiction. Sci. Rep. 4, 6189.
Bedos, M., Antaramian, A., Gonzalez-Gallardo, A., Paredes, R.G., 2019. Paced mating increases the expression of mu opioid receptors in the ventromedial hypothalamus of male rats. Behav. Brain Res. 359, 401–407.
Bonakdaran, S., Daloee, M.H., Manteghi, A.A., Akbarirad, M., Firoozi, A., Akbarirad, F., 2016. Effect of oral methadone on ECG characteristics and endocrine hormonal changes and their inter-relationship. Endocr. Metab. Immune Disord. Drug Targets 16, 168–173.
Briand Madrid, L., Morel, S., Ndiaye, K., Mezaache, S., Rojas Castro, D., Mora, M., Olivet, F., Laporte, V., Protopopescu, C., Carrieri, P., Roux, P., 2018. Factors associated with perceived loss of libido in people who inject opioids: results from a community-based survey in France. Drug Alcohol Depend. 190, 121–127.
Brown, R., Balousek, S., Mundt, M., Fleming, M., 2005. Methadone maintenance and male sexual dysfunction. J. Addict. Dis. 24, 91–106.
Bui, Q.Q., Tran, M.B., West, W.L., 1983a. Acute and subchronic effects of methadone on the blood hormonal levels of pregnant and nonpregnant Charles River CD-1 mice. Pediatr. Pharmacol. (New York) 3, 69–78.
Bui, Q.Q., Tran, M.B., West, W.L., 1983b. Evidence for hormonal imbalance after methadone treatment in pregnant and pseudopregnant rats. Proc. Soc. Exp. Biol. Med. 173, 398–407.
Carretero, J., Bodego, P., Rodriguez, R.E., Rubio, M., Blanco, E., Burks, D.J., 2004. Expression of the mu-opioid receptor in the anterior pituitary gland is influenced by age and sex. Neuropeptides 38, 63–68.
CDC, 2018. Annual Surveillance Report of Drug-Related Risks and Outcomes: United States. CDC National Center for Injury Prevention and Control, pp. 1–91.
Chekuri, V., Gerber, D., Brodie, A., Krishnadas, R., 2012. Premature ejaculation and other sexual dysfunctions in opiate dependent men receiving methadone substitution treatment. Addict. Behav. 37, 124–126.
Cheng, C.M., Lin, Y.C., Chang, K.C., 2017. Psychological distress is correlated with erectile dysfunction among patients receiving methadone maintenance in Taiwan. J. Dual Diagn. 13, 312–316.
Cicero, T.J., Bell, R.D., Wiest, W.G., Allison, J.H., Polakoski, K., Robins, E., 1975. Function of the male sex organs in heroin and methadone users. N. Engl. J. Med. 292, 882–887.
Cicero, T.J., Meyer, E.R., Bell, R.D., Koch, G.A., 1976. Effects of morphine and methadone on serum testosterone and luteinizing hormone levels and on the secondary sex organs of the male rat. Endocrinology 98, 367–372.
Clemens, J.A., Sawyer, B.D., 1974. Evidence that methadone stimulates prolactin release by dopamine receptor blockade. Endocr. Res. Commun. 1, 373–378.
Cofrancesco Jr., J., Shah, N., Ghanem, K.G., Dobs, A.S., Klein, R.S., Mayer, K., Schuman, P., Vlahov, D., Rompalo, A.M., 2006. The effects of illicit drug use and HIV infection on sex hormone levels in women. Gynecol. Endocrinol. 22, 244–251.
Colameco, S., Coren, J.S., 2009. Opioid-induced endocrinopathy. J. Am. Osteopath. Assoc. 109, 20–25.
Cushman Jr., P., 1972. Sexual behavior in heroin addiction and methadone maintenance. Correlation with plasma luteinizing hormone. N. Y. State J. Med. 72, 1261–1265.
Cushman Jr., P., 1973. Plasma testosterone in narcotic addiction. Am. J. Med. 55, 452–458.
Cushman Jr., P., Kreek, M.J., 1974. Methadone-maintained patients. Effect of methadone on plasma testosterone, FSH, LH, and prolactin. N. Y. State J. Med. 74, 1970–1973.
Dabbous, Z., Atkin, S.L., 2018. Hyperprolactinaemia in male infertility: clinical case scenarios. Arab J. Urol. 16, 44–52.
Daniell, H.W., 2002a. Hypogonadism in men consuming sustained-action oral opioids. J. Pain 3, 377–384.
Daniell, H.W., 2002b. Narcotic-induced hypogonadism during therapy for heroin addiction. J. Addict. Dis. 21, 47–53.
Daniell, H.W., 2008. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. J. Pain 9, 28–36.
De Rosa, M., Zarrilli, S., Vitale, G., Di Somma, C., Orio, F., Tauchmanova, L., Lombardi, G., Colao, A., 2004. Six months of treatment with cabergoline restores sexual potency in hyperprolactinemic males: an open longitudinal study monitoring nocturnal penile tumescence. J. Clin. Endocrinol. Metab. 89, 621–625.
Delitala, G., Grossman, A., Besser, M., 1983. Differential effects of opiate peptides and alkaloids on anterior pituitary hormone secretion. Neuroendocrinology 37, 275–279.
Estomba, H., Munoa-Hoyos, I., Gianzo, M., Urizar-Arenaza, I., Casis, L., Irazusta, J., Subiran, N., 2016. Expression and localization of opioid receptors in male germ cells and the implication for mouse spermatogenesis. PLoS One 11, e0152162.
Facchinetti, F., Comitini, G., Petraglia, F., Volpe, A., Genazzani, A.R., 1986. Reduced estriol and dehydroepiandrosterone sulphate plasma levels in methadone-addicted pregnant women. Eur. J. Obstet. Gynecol. Reprod. Biol. 23, 67–73.
Garrido, M.J., Troconiz, I.F., 1999. Methadone: a review of its pharmacokinetic/pharmacodynamic properties. J. Pharmacol. Toxicol. Methods 42, 61–66.
Gerra, G., Manfredini, M., Somaini, L., Maremmani, I., Leonardi, C., Donnini, C., 2016. Sexual dysfunction in men receiving methadone maintenance treatment: clinical history and psychobiological correlates. Eur. Addict. Res. 22, 163–175.
Ghowsi, M., Yousofvand, N., 2015. Impact of morphine dependency and detoxification by methadone on male's rat reproductive system. Iran. J. Reprod. Med. 13, 275–282.
Grattan, D.R., 2015. 60 years of neuroendocrinology: the hypothalamo-prolactin axis. J. Endocrinol. 226, T101–22.
Gronbladh, L., Ohlund, L.S., 2011. Self-reported differences in side-effects for 110 heroin addicts during opioid addiction and during methadone treatment. Heroin Addict. Relat. Clin. Probl. 13, 5–12.
Haber, P.S., Elsayed, M., Espinoza, D., Lintzeris, N., Veillard, A.S., Hallinan, R., 2017. Constipation and other common symptoms reported by women and men in methadone and buprenorphine maintenance treatment. Drug Alcohol Depend. 181, 132–139.
Hallinan, R., Byrne, A., Agho, K., McMahon, C., Tynan, P., Attia, J., 2008. Erectile dysfunction in men receiving methadone and buprenorphine maintenance treatment. J. Sex. Med. 5, 684–692.
Hallinan, R., Byrne, A., Agho, K., McMahon, C.G., Tynan, P., Attia, J., 2007. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. Int. J. Androl. 32, 131–139.
Hanbury, R., Cohen, M., Stimmel, B., 1977. Adequacy of sexual performance in men maintained on methadone. Am. J. Drug Alcohol Abuse 4, 13–20.
Hein, P.R., Schatorje, J.S., Frencken, H.J., Segers, M.F., Thomas, C.M., 1991. The effect of chronic oral methadone treatment on monkey chorionic gonadotropin, estradiol, dehydroepiandrosterone sulfate, progesterone, prolactin and cortisol levels during pregnancy in the cynomolgus monkey (Macaca fascicularis). Eur. J. Obstet. Gynecol. Reprod. Biol. 38, 145–150.
Hosseini, S.H., Isapour, A., Tavakoli, M., Taghipour, M., Rasuli, M., 2013. Erectile dysfunction in methadone maintenance patients: a cross sectional study in northern iran. Iran. J. Psychiatry 8, 172–178.
Jakubovic, A., McGeer, E.G., 1979. Narcotics and rat testicular metabolism. Mol. Pharmacol. 16, 970–980.
Johnson, J.H., Rosecrans, J.A., 1978. Blockade of the preovulatory LH surge by methadone in rats. Res. Commun. Chem. Pathol. Pharmacol. 19, 435–444.
Johnson, J.H., Rosecrans, J.A., 1980. Blockade of ovulation by methadone in the rat: a central nervous system-mediated acute effect. J. Pharmacol. Exp. Ther. 213, 110–113.
Judd, L.L., Parker, D.C., Janowsky, D.S., Segal, D.S., Risch, S.C., Huey, L.Y., 1982. The effect of methadone on the behavioral and neuroendocrine responses of manic patients. Psychiatry Res. 7, 163–170.
Kaminski, T., 2006. The involvement of protein kinases in signalling of opioid agonist FK 33-824 in porcine granulosa cells. Anim. Reprod. Sci. 91, 107–122.
Katz, N., Mazer, N.A., 2009. The impact of opioids on the endocrine system. Clin. J. Pain 25, 170–175.
Kheradmand, A., Amini Ranjbar, Z., Zeynali, Z., Sabahy, A.R., Nakhaee, N., 2015. Sleep quality and sexual function in patients under methadone maintenance treatment. Int. J. High Risk Behav. Addict. 4, e23550.
Kuhn, C.M., Bartolome, M., 1984. Effect of chronic methadone administration on neuroendocrine function in developing rats. Dev. Pharmacol. Ther. 7, 384–397.
Kuhn, C.M., Bartolome, M.B., 1985. Effect of chronic methadone administration on neuroendocrine function in young adult rats. J. Pharmacol. Exp. Ther. 234, 204–210.
Kuhn, C.M., Bartolome, M.Q., 1983. Ontogeny of endocrine responses to methadone in rats. Life Sci. 32, 1967–1974.
Lafisca, S., Bolelli, G., Franceschetti, F., Filicori, M., Flamigni, C., Marigo, M., 1981. Hormone levels in methadone-treated drug addicts. Drug Alcohol Depend. 8,

229–234.
Le Merrer, J., Becker, J.A., Befort, K., Kieffer, B.L., 2009. Reward processing by the opioid system in the brain. Physiol. Rev. 89, 1379–1412.
Llanes, C., Alvarez, A.I., Pastor, M.T., Garzon, M.A., Gonzalez-Garcia, N., Montejo, A.L., 2019. Sexual dysfunction and quality of life in chronic heroin-dependent individuals on methadone maintenance treatment. J. Clin. Med. 8, 321–333.
Lugoboni, F., Zamboni, L., Federico, A., Tamburin, S., Gruppo Inter, Sd.C.S., 2017. Erectile dysfunction and quality of life in men receiving methadone or buprenorphine maintenance treatment. A cross-sectional multicentre study. PLoS One 12, e0188994.
Mendelson, J.H., Mendelson, J.E., Patch, V.D., 1975a. Plasma testosterone levels in heroin addiction and during methadone maintenance. J. Pharmacol. Exp. Ther. 192, 211–217.
Mendelson, J.H., Meyer, R.E., Ellingboe, J., Mirin, S.M., McDougle, M., 1975b. Effects of heroin and methadone on plasma cortisol and testosterone. J. Pharmacol. Exp. Ther. 195, 296–302.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, P., 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 6, e1000097.
Murphy, M.R., 1981. Methadone reduces sexual performances and sexual motivation in the male Syrian golden hamster. Pharmacol. Biochem. Behav. 14, 561–567.
Nik Jaafar, N.R., Mislan, N., Abdul Aziz, S., Baharudin, A., Ibrahim, N., Midin, M., Das, S., Sidi, H., 2013. Risk factors of erectile dysfunction in patients receiving methadone maintenance therapy. J. Sex. Med. 10, 2069–2076.
Novick, D.M., Richman, B.L., Friedman, J.M., Friedman, J.E., Fried, C., Wilson, J.P., Townley, A., Kreek, M.J., 1993. The medical status of methadone maintenance patients in treatment for 11–18 years. Drug Alcohol Depend. 33, 235–245.
Parvaresh, N., Sabahi, A.R., Mazhari, S., Gilani, H., 2015. A study of the sexual function, sleep, and weight status of patients after 6 months of methadone maintenance treatment. Addict. Health 7, 24–29.
Plant, T.M., 2015. 60: the hypothalamo-pituitary-gonadal axis. J. Endocrinol. 226, T41–54.
Purohit, V., Singh, H.H., Ahluwalia, B.S., 1979. Evidence that the effects of methadone and marihuana on male reproductive organs are mediated at different sites in rats. Biol. Reprod. 20, 1039–1044.
Quaglio, G., Lugoboni, F., Pattaro, C., Melara, B., Mezzelani, P., Des Jarlais, D.C., 2008. Erectile dysfunction in male heroin users, receiving methadone and buprenorphine maintenance treatment. Drug Alcohol Depend. 94, 12–18.
Ragni, G., De Lauretis, L., Bestetti, O., Sghedoni, D., Gambaro, V., 1988. Gonadal function in male heroin and methadone addicts. Int. J. Androl. 11, 93–100.
Ragni, G., De Lauretis, L., Gambaro, V., Di Pietro, R., Bestetti, O., Recalcati, F., Papetti, C., 1985. Semen evaluation in heroin and methadone addicts. Acta Eur. Fertil. 16, 245–249.
Rajabizadeh, G., Yazdanpanah, F., Ramezani, M.A., 2017. The evaluation of relationship between sexual self-concept and sexual dysfunction in individuals undergoing methadone maintenance treatment. Addict. Health 9, 88–95.
Rajagopal, A., Vassilopoulou-Sellin, R., Palmer, J.L., Kaur, G., Bruera, E., 2004. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer 100, 851–858.
Ray, J.A., Kushnir, M.M., Meikle, A.W., Sindt, J.E., Strathmann, F.G., 2017. An exploratory study evaluating the impact of opioid and non-opioid pain medications on serum/plasma free testosterone and free estradiol concentrations. Drug Test. Anal. 9, 1555–1560.
Rolandi, E., Barreca, T., 1978. Effects of two analgesic opiates (methadone and pentazocine) on the serum prolactin levels in breast cancer. Acta Endocrinol. (Copenh.) 88, 452–454.
SAMHSA, 2018. Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53).
Shaar, C.J., Clemens, J.A., 1980. The effects of opiate agonists on growth hormone and prolactin release in rats. Fed. Proc. 39, 2539–2543.
Shaw, N.D., Histed, S.N., Srouji, S.S., Yang, J., Lee, H., Hall, J.E., 2010. Estrogen negative feedback on gonadotropin secretion: evidence for a direct pituitary effect in women. J. Clin. Endocrinol. Metab. 95, 1955–1961.
Sheridan, P.J., 1978. Effects of morphine and methadone on the nuclear uptake of estradiol by the brain. Clin. Toxicol. 13, 383–390.
Singh, H.H., Purohit, V., Ahluwalia, B.S., 1982. Methadone blocks dopamine-mediated release of gonadotropins in rat hypothalamus. Neuroendocrinology 34, 347–352.
Smith, H.S., Elliott, J.A., 2012. Opioid-induced androgen deficiency (OPIAD). Pain Physician 15, ES145–ES156.
Soyka, L.F., Joffe, J.M., Peterson, J.M., Smith, S.M., 1978. Chronic methadone administration to male rats: tolerance to adverse effects on sires and their progeny. Pharmacol. Biochem. Behav. 9, 405–409.
Spagnolli, W., De Venuto, G., Mattarei, M., Dal Ri, P., Miori, R., 1987. Prolactin and thyrotropin pituitary response to thyrotropin releasing hormone in young female heroin addicts. Drug Alcohol Depend. 20, 247–254.
Spring Jr., W.D., Willenbring, M.L., Maddux, T.L., 1992. Sexual dysfunction and psychological distress in methadone maintenance. Int. J. Addict. 27, 1325–1334.
Teoh, J.B., Yee, A., Danaee, M., Ng, C.G., Sulaiman, A.H., 2017. Erectile dysfunction among patients on methadone maintenance therapy and its association with quality of life. J. Addict. Med. 11, 40–46.
Thomas, J.A., Dombrosky, J.T., 1975. Effect of methadone on the male reproductive system. Arch. Int. Pharmacodyn. Ther. 215, 215–221.
Thomas, J.A., Shahid-Salles, K.S., Donovan, M.P., 1977. Effects of narcotics on the reproductive system. Adv. Sex Horm. Res. 3, 169–195.
Trajanovska, A.S., Vujovic, V., Ignjatova, L., Janicevic-Ivanovska, D., Cibisev, A., 2013. Sexual dysfunction as a side effect of hyperprolactinemia in methadone maintenance therapy. Med. Arch. 67, 48–50.
Varma, A., Sapra, M., Iranmanesh, A., 2018. Impact of opioid therapy on gonadal hormones: focus on buprenorphine. Horm. Mol. Biol. Clin. Investig. 36.
Willenbring, M.L., Morley, J.E., Krahn, D.D., Carlson, G.A., Levine, A.S., Shafer, R.B., 1989. Psychoneuroendocrine effects of methadone maintenance. Psychoneuroendocrinology 14, 371–391.
Wittert, G., Hope, P., Pyle, D., 1996. Tissue distribution of opioid receptor gene expression in the rat. Biochem. Biophys. Res. Commun. 218, 877–881.
Wolff, K., Hay, A.W., Raistrick, D., Calvert, R., 1993. Steady-state pharmacokinetics of methadone in opioid addicts. Eur. J. Clin. Pharmacol. 44, 189–194.
Woody, G., McLellan, A.T., O'Brien, C., Persky, H., Stevens, G., Arndt, I., Carroff, S., 1988. Hormone secretion in methadone-dependent and abstinent patients. NIDA Res. Monogr. 81, 216–223.
Xia, Y., Zhang, D., Li, X., Chen, W., He, Q., Jahn, H.J., Li, X., Chen, J., Hu, P., Ling, L., 2013. Sexual dysfunction during methadone maintenance treatment and its influence on patient's life and treatment: a qualitative study in South China. Psychol. Health Med. 18, 321–329.
Yee, A., Loh, H.S., Hisham Hashim, H.M., Ng, C.G., 2014. Clinical factors associated with sexual dysfunction among men in methadone maintenance treatment and buprenorphine maintenance treatment: a meta-analysis study. Int. J. Impot. Res. 26, 161–166.
Zhang, M., Zhang, H., Shi, C.X., McGoogan, J.M., Zhang, B., Zhao, L., Zhang, M., Rou, K., Wu, Z., 2014. Sexual dysfunction improved in heroin-dependent men after methadone maintenance treatment in Tianjin, China. PLoS One 9, e88289.
Zhang, Y., Wang, P., Ma, Z., Xu, Z., Li, Y., 2011. Sexual function of 612 male addicts treated by methadone. J. Cent. South Univ. (Med. Sci.) 36, 739–743.