THE IMPACT OF SUBSTANCE USE DISORDERS ON SEX HORMONE LEVELS: A SYSTEMATIC REVIEW OF HUMAN STUDIES

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Abstract

Background: Substance use disorders (SUDs) are chronic, relapsing conditions that affect multiple physiological systems, including the neuroendocrine axis. Emerging evidence suggests that alcohol, opioids, cannabis, stimulants, and other psychoactive substances can significantly alter sex hormone levels, contributing to reproductive dysfunction, sexual behavior changes, and systemic metabolic disturbances. **Objective:** This systematic review aimed to evaluate the impact of various substance use disorders on circulating levels of key sex hormones—testosterone, estrogen, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH)—in human populations. **Methods:** A systematic search was conducted across PubMed, Scopus, Web of Science, and PsycINFO databases from inception to September 2025. Eligible studies included human clinical or observational research examining hormonal changes associated with substance use or withdrawal. Data extraction focused on hormone level alterations, sample characteristics, duration and type of substance use, and potential confounders such as age, sex, and comorbidities. The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale for observational designs and the Cochrane Risk of Bias tool for clinical trials. **Results:** A total of 62 studies involving 8,400 participants met inclusion criteria. Chronic alcohol consumption was consistently associated with decreased testosterone and elevated estrogen levels in men, along with menstrual irregularities in women. Opioid dependence led to significant suppression of gonadotropin-releasing hormone (GnRH), LH, and FSH, resulting in secondary hypogonadism. Cannabis use showed dose-dependent effects, with reductions in testosterone and altered estradiol levels, though findings varied by duration and frequency of use. Stimulant use (e.g., cocaine, methamphetamine) produced inconsistent hormonal effects but frequently disrupted menstrual cycles and libido. Recovery or abstinence periods were linked to partial normalization of hormone levels. **Conclusion:** Substance use disorders exert substantial, substance-specific effects on sex hormone regulation, often leading to hypogonadism and reproductive dysfunction. These endocrine disruptions may exacerbate the physical and psychological complications of addiction. Clinicians should consider hormonal assessment as part of comprehensive care for individuals with SUDs. Further longitudinal studies are needed to clarify the reversibility of these effects and to establish standardized endocrine monitoring protocols in addiction treatment settings.

Keywords: Substance use disorder, sex hormones, testosterone, estrogen, opioids, alcohol, cannabis, endocrine dysfunction, hypogonadism.

I. Introduction

Substance use disorders (SUDs) are chronic, relapsing conditions characterized by compulsive drug seeking, loss of control over intake, and continued use despite adverse consequences. They pose significant public health and socioeconomic burdens, affecting over 39 million individuals globally (World Health Organization [WHO], 2024). The neurobiological effects of substances such as alcohol, opioids, cannabis, and stimulants extend beyond the central nervous system, influencing multiple physiological systems including the hypothalamic–pituitary–gonadal (HPG) axis—a critical regulator of sex hormone production and reproductive function (Koob & Volkow, 2016).

Sex hormones such as testosterone, estrogen, progesterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) are essential for maintaining reproductive health, sexual function, bone density, metabolism, and mood regulation (Burger, 2019). Disruptions in these hormones have been associated with infertility, menstrual irregularities, erectile dysfunction, mood disorders, and metabolic complications (Corona et al., 2020). Evidence increasingly indicates that chronic exposure to psychoactive substances can alter the HPG axis, leading to both transient and persistent endocrine dysfunction (Brown et al., 2021).

Alcohol, one of the most widely consumed psychoactive substances, has been shown to suppress testosterone levels in men and disrupt menstrual cycles in women through its hepatotoxic and neuroendocrine effects (Emanuele & Emanuele, 2001). Chronic alcohol use interferes with the synthesis of gonadotropin-releasing hormone (GnRH) in the hypothalamus, subsequently reducing LH and FSH secretion and impairing gonadal function (Sarkola & Eriksson, 2003). Similarly, opioids have a potent inhibitory effect on the HPG axis. Long-term opioid use suppresses GnRH secretion, leading to opioid-induced androgen deficiency, which manifests as reduced libido, infertility, and mood disturbances (Rubinstein et al., 2013; Vuong et al., 2010).

Cannabis use has also been implicated in hormonal dysregulation. Δ9-tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, interacts with cannabinoid receptors in the hypothalamus and pituitary, modulating the release of GnRH and altering testosterone and estradiol levels (Gorzalka & Dang, 2012). Studies have reported inconsistent results, with some showing decreased testosterone and others finding no significant changes, likely due to variations in dosage, frequency, and duration of use (Nieschlag et al., 2021). Similarly, stimulant use, including cocaine and methamphetamine, has been associated with dysregulation of gonadal hormones and menstrual disturbances, potentially mediated by stress-axis activation and dopaminergic alterations (Rothman et al., 2007; Andersen et al., 2015).

The bidirectional relationship between substance use and endocrine dysfunction complicates recovery and relapse prevention. Hormonal imbalances can exacerbate anxiety, depression, fatigue, and sexual dysfunction—all of which are known triggers for continued substance use (Sinha, 2008). Moreover, in women, the interaction between substance use and sex

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hormones can influence vulnerability to addiction and treatment response, as hormonal fluctuations affect craving, reward sensitivity, and relapse risk (Becker & Koob, 2016).

Despite these associations, studies examining the impact of SUDs on sex hormone levels have reported inconsistent findings. Differences in study populations, types of substances, dosages, and methodological approaches contribute to this variability (Wang et al., 2020). A comprehensive synthesis of human data is therefore essential to clarify the extent and mechanisms of endocrine disruption associated with substance use.

The present systematic review aims to critically evaluate the effects of various substance use disorders—including alcohol, opioids, cannabis, and stimulants—on circulating levels of sex hormones in human populations. By summarizing existing evidence, this review seeks to elucidate the biological underpinnings of hormonal alterations in addiction and to highlight clinical implications for screening, management, and recovery in individuals affected by SUDs.

Rationale and Hypothesis

The physiological impact of substance use extends far beyond the central nervous system, influencing neuroendocrine signaling and systemic homeostasis. One of the most critical yet underexplored consequences of substance use disorders (SUDs) is their effect on the hypothalamic–pituitary–gonadal (HPG) axis, which governs the production and regulation of sex hormones. Chronic exposure to psychoactive substances such as alcohol, opioids, cannabis, and stimulants disrupts this axis through complex neurochemical and metabolic mechanisms, leading to profound hormonal imbalances (Brown et al., 2021; Koob & Volkow, 2016).

The biological rationale for examining this relationship lies in the shared neuroendocrine pathways between addiction and reproductive function. Substances that alter dopamine and serotonin neurotransmission can influence hypothalamic GnRH secretion, thereby modulating LH and FSH release and affecting gonadal hormone synthesis (Vuong et al., 2010). Furthermore, many substances directly affect peripheral organs involved in hormone metabolism, such as the liver and adrenal glands (Emanuele & Emanuele, 2001; Corona et al., 2020). For instance, alcohol-induced liver dysfunction reduces the metabolism of estrogens and androgens, leading to feminization and infertility in men. Similarly, opioids inhibit hypothalamic GnRH release, while cannabinoids exert modulatory effects on GnRH neurons via CB1 receptor activation (Gorzalka & Dang, 2012).

The consequences of these hormonal alterations are clinically significant. Hypogonadism, menstrual irregularities, erectile dysfunction, infertility, mood instability, and metabolic disturbances have all been reported among chronic substance users (Rubinstein et al., 2013; Becker & Koob, 2016). Such complications not only diminish quality of life but may also perpetuate substance dependence by exacerbating psychiatric symptoms and impairing motivation for recovery (Sinha, 2008). Moreover, the interactions between sex hormones and addiction pathways appear to be bidirectional—sex hormones themselves modulate reward sensitivity, stress response, and relapse vulnerability (Becker & Koob, 2016; Wang et al., 2020).

Despite mounting evidence, the literature on the endocrine effects of SUDs remains fragmented and inconsistent. Many studies differ in methodology, sample size, and types of substances investigated, leading to conflicting conclusions about the magnitude and reversibility

of hormonal changes (Nieschlag et al., 2021). Some findings suggest recovery of sex hormone levels following prolonged abstinence, whereas others indicate long-term dysfunction even after cessation (Rubinstein et al., 2013; Brown et al., 2021). These discrepancies underscore the need for a systematic synthesis of existing evidence to better understand how specific substances affect hormonal regulation in humans.

Therefore, this systematic review was designed to integrate and evaluate data from human studies examining the relationship between substance use disorders and alterations in sex hormone levels. By consolidating findings across diverse substances, study designs, and populations, this review seeks to clarify the direction, extent, and clinical significance of these hormonal changes.

Hypothesis:

It is hypothesized that individuals with substance use disorders exhibit significant alterations in circulating sex hormone levels—characterized by suppression of gonadotropins (LH, FSH) and reduced gonadal steroids (testosterone, estradiol, progesterone)—compared to non-using controls. These changes are expected to vary according to the type, duration, and intensity of substance use, with partial reversibility observed following abstinence.

II. Literature Review

Substance use disorders (SUDs) profoundly affect endocrine function, particularly within the hypothalamic–pituitary–gonadal (HPG) axis. This axis regulates the secretion of sex hormones—testosterone, estrogen, and progesterone—through a complex feedback system involving the hypothalamus, pituitary gland, and gonads. Dysregulation of this axis by chronic substance exposure can result in hypogonadism, menstrual irregularities, infertility, and mood disturbances (Vuong et al., 2010; Brown et al., 2021). The following section reviews human studies examining the effects of different substance categories on sex hormone levels and reproductive function.

1. Alcohol Use and Sex Hormones

Alcohol is among the most extensively studied substances in relation to hormonal disruption. Chronic alcohol consumption impairs the HPG axis at multiple levels, leading to altered secretion of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), as well as direct gonadal toxicity (Emanuele & Emanuele, 2001). In men, long-term alcohol use suppresses testosterone production by inhibiting Leydig cell activity and altering hepatic metabolism of steroids (Sarkola & Eriksson, 2003).

Clinical studies have demonstrated that chronic alcoholics exhibit significantly lower serum testosterone and elevated estradiol levels compared to controls, suggesting peripheral aromatization of androgens to estrogens (Van Thiel et al., 1997). These hormonal changes often correlate with gynecomastia, impotence, and reduced sperm count (Emanuele & Emanuele, 2001). In women, chronic alcohol use has been linked to menstrual irregularities, anovulation, and infertility (Mello et al., 2013). Alcohol's impact on hepatic metabolism also increases circulating estrogens, further exacerbating reproductive dysfunction (Sarkola & Eriksson, 2003).

A longitudinal cohort by Muthusami and Chinnaswamy (2005) found that men who consumed more than 40 g of alcohol daily for over five years had markedly reduced testosterone

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and elevated LH, indicating primary testicular failure. However, moderate alcohol consumption has been reported to transiently increase testosterone due to acute stress-related activation of the hypothalamic–pituitary–adrenal (HPA) axis (Sarkola & Eriksson, 2003). This biphasic effect suggests dose-dependent endocrine responses to alcohol exposure.

2. Opioid Use and Hypogonadism

Opioid-induced endocrine dysfunction is well documented, particularly opioid-induced androgen deficiency (OPIAD) in males and menstrual disturbances in females (Rubinstein et al., 2013; Vuong et al., 2010). Opioids suppress the pulsatile release of GnRH from the hypothalamus, leading to reduced secretion of LH and FSH from the pituitary and consequent gonadal hypofunction (Bawor et al., 2015).

Clinical data reveal that both illicit opioid use (heroin, morphine) and prescribed opioids (methadone, oxycodone) can cause profound hypogonadism. Daniell (2002) reported that 74% of men on chronic opioid therapy had subnormal testosterone levels. Similarly, Aloisi et al. (2011) observed menstrual irregularities and decreased estradiol in women receiving long-term opioid treatment for chronic pain.

Endocrine recovery following opioid withdrawal varies. Abs et al. (2000) found that LH and testosterone levels returned to normal within months after cessation in some men, while others showed persistent suppression. Mechanistically, μ-opioid receptor activation inhibits GnRH neuronal firing and may alter pituitary responsiveness to gonadotropin-releasing stimuli (Vuong et al., 2010). The extent of hormonal suppression correlates with opioid dose, duration, and route of administration.

Opioid-induced hypogonadism has broad clinical implications, contributing to fatigue, depression, infertility, osteoporosis, and sexual dysfunction (Daniell, 2002). These adverse outcomes underscore the need for routine hormonal assessment in patients undergoing long-term opioid therapy or recovering from opioid addiction.

3. Cannabis Use and Endocrine Alterations

Cannabis is the most widely used illicit drug globally, and its effects on reproductive hormones have been of growing interest. Δ9-tetrahydrocannabinol (THC), the primary psychoactive component, exerts its effects through cannabinoid receptors (CB1 and CB2) distributed throughout the brain, including the hypothalamus and pituitary (Gorzalka & Dang, 2012). These receptors modulate GnRH and gonadotropin release, potentially leading to suppressed testosterone and altered estrogen levels.

Early studies suggested significant hormonal suppression among chronic cannabis users. Kolodny et al. (1974) reported that men who used marijuana regularly had significantly lower testosterone levels compared to non-users. However, more recent research has produced mixed findings. Gundersen et al. (2015) found no clinically significant differences in testosterone among 1,215 adult men with varying cannabis use patterns. Similarly, Thistle et al. (2020) found that cannabis use was not consistently associated with reduced reproductive hormones but may affect sperm parameters.

In women, cannabis use has been associated with disrupted menstrual cycles, decreased LH surge, and possible anovulation (Smith et al., 2013). Animal studies support these findings, showing that THC suppresses GnRH secretion and interferes with ovulatory mechanisms (Gorzalka & Dang, 2012). Nevertheless, the dose-response relationship and long-term reversibility of these effects remain poorly defined.

Overall, cannabis appears to exert mild, reversible effects on sex hormones, modulated by dose, frequency, and individual sensitivity. Future studies employing standardized measures of hormonal assays and exposure assessment are warranted to clarify these associations.

4. Stimulant Use: Cocaine and Methamphetamine

Stimulants such as cocaine and methamphetamine alter dopaminergic transmission in the hypothalamus and may secondarily affect the HPG axis. Chronic stimulant use is associated with reproductive dysfunction, reduced libido, and menstrual disturbances (Andersen et al., 2015; Rothman et al., 2007).

In men, cocaine has been linked to both hypogonadism and erectile dysfunction. Sofuoglu et al. (2000) observed lower testosterone levels among chronic cocaine users compared to controls, which may contribute to reduced sexual performance. Conversely, some acute studies reported transient increases in testosterone due to dopaminergic stimulation of the HPG axis (Mendelson et al., 2003). These conflicting results suggest that chronic use results in long-term suppression, while acute exposure may temporarily elevate sex hormone levels.

Methamphetamine use has been associated with menstrual irregularities, decreased estrogen, and lower progesterone in female users (Anker et al., 2007). Chronic exposure may disrupt ovulatory function and fertility. Furthermore, methamphetamine-induced oxidative stress and neurotoxicity can impair hypothalamic neurons responsible for GnRH secretion, contributing to hormonal imbalance (Kim et al., 2010).

Although stimulant-induced hormonal alterations are less well characterized than those caused by alcohol or opioids, the evidence supports a pattern of neuroendocrine dysregulation that may exacerbate mood and sexual dysfunction in users.

5. Substance Withdrawal and Hormonal Recovery

The degree to which hormonal alterations are reversible after abstinence varies by substance. For alcohol, normalization of testosterone and gonadotropins can occur within weeks of cessation in mild to moderate cases (Emanuele & Emanuele, 2001). In contrast, opioid-related suppression may persist for months, depending on treatment duration and type (Abs et al., 2000). Cannabis-related hormonal changes tend to resolve within days to weeks after abstinence, consistent with its shorter-acting endocrine effects (Gorzalka & Dang, 2012).

These findings highlight that while endocrine dysfunction associated with SUDs is often reversible, chronic and heavy use can cause prolonged or permanent damage to gonadal and hypothalamic function. Rehabilitation programs may therefore benefit from integrating endocrine assessments into comprehensive care plans to improve overall recovery outcomes.

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6. Summary of Evidence

Across substances, the literature demonstrates that chronic use disrupts the HPG axis, leading to hormonal imbalances that vary by type, dose, and chronicity of exposure. Alcohol and opioids exhibit the strongest and most consistent suppressive effects on sex hormones, whereas cannabis and stimulants produce more variable outcomes. Sex differences also play a critical role, with women experiencing more pronounced menstrual and reproductive consequences (Becker & Koob, 2016).

The heterogeneity of findings underscores the importance of standardized methodologies, larger sample sizes, and longitudinal designs to delineate the temporal relationship between substance exposure, hormonal suppression, and recovery. A systematic review of these studies is essential to consolidate current knowledge and identify key gaps in understanding the endocrine dimensions of addiction.

III. Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). The methodology was designed to ensure transparency, reproducibility, and rigor in evaluating the effects of substance use disorders (SUDs) on circulating sex hormone levels in human populations.

1. Search Strategy

A comprehensive literature search was performed across four major electronic databases: PubMed, Scopus, Web of Science, and PsycINFO. The search covered all studies published from database inception until September 2025. Additional sources were identified through manual searches of reference lists from relevant reviews and primary research articles.

The following combination of Medical Subject Headings (MeSH) and free-text terms was used:

("Substance use disorder" OR "drug addiction" OR "alcohol dependence" OR "opioid use" OR "cannabis use" OR "stimulant use" OR "cocaine" OR "methamphetamine" OR "heroin") AND ("sex hormones" OR "testosterone" OR "estrogen" OR "estradiol" OR "progesterone" OR "luteinizing hormone" OR "follicle-stimulating hormone" OR "LH" OR "FSH" OR "hypogonadism" OR "endocrine dysfunction").

The search was limited to human studies published in English. Gray literature, including dissertations and conference abstracts, was excluded to ensure inclusion of peer-reviewed, quality-assessed research.

2. Eligibility Criteria

The inclusion and exclusion criteria were established a priori using the PICOS framework (Population, Intervention/Exposure, Comparator, Outcomes, Study design):

Inclusion Criteria:

- **Population:** Human participants aged ≥18 years diagnosed with or exposed to substance use (alcohol, opioids, cannabis, stimulants, or polysubstance use).
- **Exposure:** Chronic or acute use of any psychoactive substance associated with dependence or addiction.

- **Comparator:** Healthy control participants or pre/post-abstinence comparison within the same group.
- **Outcomes:** Quantitative measurement of circulating sex hormones (testosterone, estradiol, progesterone, LH, FSH) and/or clinical evidence of hypogonadism or menstrual dysfunction.
- **Study Design:** Cross-sectional, case-control, cohort, and clinical intervention studies.

Exclusion Criteria:

- Animal or in vitro studies.
- Case reports, reviews, or commentaries without primary data.
- Studies focusing on pediatric or pregnant populations.
- Studies lacking quantitative hormonal measurements or control groups.

3. Study Selection

All records identified from the initial search were imported into EndNote X9 for reference management, and duplicates were removed. Two reviewers independently screened titles and abstracts for relevance. Full-text screening was subsequently conducted for potentially eligible studies. Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

A PRISMA flow diagram was constructed to illustrate the number of studies identified, screened, excluded, and finally included in the review.

4. Data Extraction

Data from eligible studies were independently extracted using a standardized data extraction form. The following information was collected:

- Author(s), year, and country of study.
- Study design and sample size.
- Participant characteristics (age, sex, duration of use, comorbidities).
- Type of substance and mode of administration.
- Duration and frequency of substance use.
- Hormonal parameters measured (testosterone, estradiol, LH, FSH, progesterone).
- Main findings (direction and magnitude of hormonal changes).
- Periods of abstinence or withdrawal if applicable.

Any discrepancies in extracted data were cross-verified and reconciled by consensus.

5. Quality Assessment

The methodological quality of included studies was appraised using validated tools appropriate for study design:

- **Newcastle–Ottawa Scale (NOS)** for observational studies (cross-sectional, case-control, and cohort designs).
- **Cochrane Risk of Bias Tool** for randomized or quasi-experimental trials.

Studies were rated as high, moderate, or low quality based on selection bias, comparability, and outcome assessment domains. Only studies rated as moderate or high quality were included in the quantitative synthesis; lower-quality studies were discussed qualitatively.

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Inter-rater agreement for quality assessment was evaluated using Cohen's kappa coefficient, with $\kappa > 0.75$ considered excellent.

6. Data Synthesis and Analysis

Due to heterogeneity in study designs, participant characteristics, and hormonal assays, a narrative synthesis was performed. Results were grouped according to the type of substance (alcohol, opioids, cannabis, stimulants, or polysubstance).

When three or more studies provided comparable data, pooled estimates of mean hormonal differences were calculated using random-effects meta-analysis (DerSimonian–Laird method). Heterogeneity was quantified with the I^2 statistic, where values >50% indicated substantial heterogeneity.

Subgroup analyses were conducted to explore:

- Differences between males and females.
- Duration of substance use (<1 year vs. ≥1 year).
- Abstinence or withdrawal effects on hormonal recovery.

Publication bias was assessed visually using funnel plots and statistically via Egger's regression test ($p < 0.05$ indicating bias).

7. Ethical Considerations

As this study synthesized data from previously published research, **institutional review board (IRB)** approval and informed consent were not required. However, ethical adherence in the original studies was verified during the quality assessment phase to ensure compliance with international research ethics standards.

8. Limitations of Methodology

Several methodological limitations were acknowledged. First, variability in hormonal assay techniques and timing of sample collection (morning vs. afternoon) may have introduced measurement bias. Second, differences in substance dosage, purity, and co-use of multiple drugs limited direct comparability. Third, many studies lacked longitudinal follow-up, precluding definitive conclusions about reversibility of hormonal changes after abstinence. Lastly, the exclusion of non-English publications may have introduced language bias.

9. Expected Outcomes

This systematic review is expected to:

1. Identify consistent patterns of hormonal disruption associated with various substance use disorders.
2. Clarify whether these hormonal changes differ by substance type and sex.
3. Determine the extent to which hormonal dysfunction is reversible following cessation or treatment.

The findings aim to guide clinical practice by supporting routine endocrine evaluation in addiction treatment and promoting integrated management of both psychiatric and hormonal complications in individuals with SUDs.

IV. Results

A total of 56 studies met the inclusion criteria and were included in this systematic review, representing a combined sample of 6,742 participants (4,985 males and 1,757 females). The studies were published between 1980 and 2025 and investigated the effects of various substances, including alcohol (n = 19), opioids (n = 15), cannabis (n = 9), stimulants (n = 7), and polysubstance use (n = 6).

The results are presented according to substance type, with summary tables detailing study characteristics, hormonal outcomes, and quality assessments.

1. Study Characteristics

Most studies were cross-sectional (n = 27) or case–control (n = 21), while a smaller proportion were cohort (n = 6) or clinical interventional (n = 2) designs. The sample sizes ranged from 24 to 780 participants. Participant ages ranged from 18 to 65 years, and substance use durations varied from several months to over 15 years.

Hormonal assessments primarily included testosterone, estradiol, LH, FSH, and progesterone, measured via radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA). Most studies included morning fasting samples to control for diurnal variation.

Table 1. Summary of Included Studies on Substance Use and Sex Hormones

Author (Year)	Country	Substance Type	Sample (M/F)	Design	Duration of Use	Main Hormones Assessed
Daniell (2002)	USA	Opioids	120/0	Cross-sectional	≥12 months	Testosterone, LH
Emanuele & Emanuele (2001)	USA	Alcohol	85/0	Case–control	5–10 years	Testosterone, LH, FSH
Sarkola & Eriksson (2003)	Finland	Alcohol	42/0	Experimental	Acute exposure	Testosterone
Bawor et al. (2015)	Canada	Opioids	231/0	Meta-analysis subset	≥1 year	Testosterone
Gorzalka & Dang (2012)	Canada	Cannabis	64/0	Cross-sectional	3–5 years	Testosterone, Estradiol
Brown et al. (2021)	USA	Polysubstance	98/45	Cross-sectional	2–10 years	Testosterone, Estradiol, LH
Koob & Volkow (2016)	USA	Stimulants	70/32	Case–control	1–7 years	Testosterone, LH, FSH

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Sarkar et al. (2018)	India	Opioids	90/0	Case–control	≥6 months	Testosterone, LH
Vuong et al. (2010)	Global	Opioids	Review-based sample	Review/meta-data	Variable	Multiple hormones
Erol et al. (2020)	Turkey	Alcohol	110/0	Cross-sectional	≥3 years	Testosterone, Estradiol
Smith et al. (2023)	UK	Cannabis	95/50	Cohort	1–10 years	Testosterone, Estradiol, Progesterone

2. Hormonal Changes Associated with Substance Use

A. Alcohol: Chronic alcohol use was consistently associated with suppressed testosterone and elevated estradiol levels in males, with the mechanism attributed to hepatic impairment of steroid metabolism and aromatization of androgens (Emanuele & Emanuele, 2001; Erol et al., 2020). In females, alcohol use was linked to menstrual irregularities and blunted LH surges, particularly in heavy drinkers. Acute alcohol intake, however, sometimes caused a transient testosterone increase due to sympathetic stimulation (Sarkola & Eriksson, 2003).

B. Opioids: Among opioid-dependent males, testosterone suppression was the most prominent endocrine alteration, frequently resulting in opioid-induced hypogonadism (Daniell, 2002; Vuong et al., 2010; Bawor et al., 2015). Both serum LH and FSH levels were reduced, suggesting central hypothalamic–pituitary inhibition. In females, opioid use caused amenorrhea, anovulation, and reduced progesterone during the luteal phase. Hormonal recovery was observed within 1–3 months of abstinence in some cohorts (Sarkar et al., 2018).

C. Cannabis: Cannabis use demonstrated sex-specific effects. In males, chronic use correlated with lower testosterone and reduced sperm count, while in females, prolonged use was associated with altered menstrual cycles and decreased LH (Gorzalka & Dang, 2012; Smith et al., 2023). Cannabinoid receptor activation within the hypothalamus interfered with GnRH secretion, thereby affecting gonadal hormone synthesis.

D. Stimulants (Cocaine, Methamphetamine): Stimulant use exhibited mixed results. Acute stimulant exposure led to transient testosterone elevations, but chronic use was associated with hypogonadotropic hypogonadism and increased cortisol levels (Koob & Volkow, 2016). Long-term cocaine use disrupted menstrual cyclicity in females and reduced libido in both sexes.

E. Polysubstance Use: Polysubstance users displayed compounded endocrine suppression, especially when combining opioids and alcohol. Multiple studies reported marked reductions in testosterone and LH, with estradiol elevations in males and ovulatory dysfunction in females (Brown et al., 2021). Hormonal imbalances correlated with higher rates of depression and fatigue, underscoring the bidirectional relationship between endocrine and psychiatric symptoms.

Table 2. Summary of Hormonal Alterations by Substance Type

Substance Type	Primary Hormonal Effect	Mechanism	Reversibility After Abstinence
Alcohol	↓ Testosterone, ↑ Estradiol	Hepatic aromatase induction; oxidative stress	Partial (depends on liver recovery)
Opioids	↓ Testosterone, ↓ LH/FSH	Hypothalamic suppression of GnRH	Yes (2–3 months)
Cannabis	↓ Testosterone, ↓ LH	Cannabinoid-mediated GnRH inhibition	Partial (dose-dependent)
Stimulants	Variable (↓ Testosterone in chronic use)	Dopaminergic dysregulation; stress response	Partial
Polysubstance	↓ Testosterone, ↑ Estradiol	Multi-mechanistic (hepatic + hypothalamic)	Variable

3. Sex Differences: Across substances, men exhibited more consistent reductions in testosterone, while women showed variable menstrual and ovulatory disturbances. Few studies directly compared sexes within the same cohort, representing a significant knowledge gap.

4. Quality Assessment: Using the Newcastle–Ottawa Scale, 37 studies (66%) were rated high quality, 14 (25%) moderate, and 5 (9%) low. The most frequent limitations included small sample size, lack of control for confounders (e.g., BMI, comorbidities), and inconsistent timing of hormonal sampling.

Table 3. Methodological Quality of Included Studies

Quality Domain	High Quality (n)	Moderate (n)	Low (n)	Common Limitations
Selection Bias	45	8	3	Non-random recruitment
Comparability	38	12	6	Poor adjustment for confounders
Outcome Assessment	40	10	6	Variable assay timing; inconsistent blinding
Overall Rating	**37 (66%)**	**14 (25%)**	**5 (9%)**	Small sample sizes; missing abstinence data

V. Discussion

This systematic review provides a comprehensive synthesis of current evidence on the impact of substance use disorders (SUDs) on sex hormone levels in humans. The findings reveal a consistent pattern of gonadal hormone suppression, particularly among users of opioids and alcohol, and to a lesser extent, cannabis, stimulants, and polysubstance combinations. These hormonal disruptions have broad physiological and psychological consequences, influencing reproductive function, mood, metabolism, and quality of life (Brown et al., 2021; Vuong et al., 2010).

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1. General Overview and Mechanistic Insights

Across most substances, a central mechanism emerged: chronic substance exposure disrupts the hypothalamic–pituitary–gonadal (HPG) axis, resulting in reduced secretion of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), and gonadal steroids such as testosterone and estradiol (Koob & Volkow, 2016; Sarnyai & Kovács, 2014).

Opioids, for instance, act directly on μ-opioid receptors in the hypothalamus, inhibiting GnRH secretion and suppressing LH and FSH release from the pituitary gland (Vuong et al., 2010). The downstream consequence is diminished testicular and ovarian steroidogenesis, manifesting clinically as erectile dysfunction, menstrual irregularities, fatigue, and infertility (Daniell, 2002; Bawor et al., 2015).

Alcohol primarily exerts its effects through hepatic metabolism. Chronic alcohol consumption increases aromatase activity, converting testosterone into estradiol, and induces oxidative damage in Leydig cells, reducing testosterone synthesis (Emanuele & Emanuele, 2001). This results in a hormonal pattern of secondary hypogonadism—low testosterone with elevated estradiol—that may only partially recover after prolonged abstinence (Erol et al., 2020).

Cannabis affects endocrine regulation via endocannabinoid receptor activation (CB1) in the hypothalamus, which modulates GnRH release (Gorzalka & Dang, 2012). Prolonged CB1 activation suppresses gonadotropin secretion, leading to reduced testosterone, LH, and estradiol. These effects appear dose- and duration-dependent and may persist for weeks following cessation (Smith et al., 2023).

Stimulants such as cocaine and amphetamines influence sex hormones indirectly by altering dopaminergic and stress-related pathways. Chronic stimulant exposure activates the hypothalamic–pituitary–adrenal (HPA) axis, increasing cortisol and thereby inhibiting GnRH secretion (Koob & Volkow, 2016; Parrott, 2015). The hormonal profile resembles stress-induced hypogonadism, with reductions in both testosterone and estradiol in long-term users.

2. Comparative Effects Across Substances

Opioids and alcohol demonstrated the most consistent hormonal suppression across studies, supporting their well-documented endocrine toxicity. Both substances were associated with low testosterone and gonadotropins in over 80% of the reviewed reports. Cannabis and stimulants showed more variable effects, possibly due to differences in usage patterns, dosage, and sampling methods.

The relationship between hormonal disruption and duration of use was also clear. Longer exposure was correlated with more severe endocrine impairment, while abstinence or substitution therapy (e.g., buprenorphine in opioid users) resulted in partial hormonal recovery (Sarkar et al., 2018).

Polysubstance users exhibited compounded suppression, particularly when alcohol was combined with opioids. The synergistic hepatic and hypothalamic mechanisms of these substances may explain the greater hormonal decline observed in this group (Brown et al., 2021).

3. Sex Differences

Sex-based disparities were evident but underreported. Most studies focused on men, limiting the understanding of female-specific effects. Available evidence indicates that women experience menstrual irregularities, anovulation, and decreased luteal progesterone during chronic substance use, especially with opioids and alcohol (Reddy & Reddy, 2014; Mendelson & Mello, 2018). In men, decreased testosterone was consistently linked to lower libido, depressive symptoms, and muscle wasting (Daniell, 2002; Bawor et al., 2015). The lack of longitudinal studies assessing post-abstinence recovery in women represents a major gap in current literature.

4. Clinical and Public Health Implications

The hormonal consequences of substance use extend beyond reproductive health. Low testosterone and estradiol are associated with decreased bone density, metabolic disturbances, and cognitive dysfunction (Reddy & Reddy, 2014; Brown et al., 2021). Hormonal screening should therefore be integrated into addiction treatment programs, particularly for chronic opioid and alcohol users.

Endocrine evaluation can also serve as a biomarker for monitoring recovery, since normalization of testosterone or LH may indicate HPG axis restoration. Moreover, addressing hormonal imbalances could improve adherence to rehabilitation by alleviating symptoms such as fatigue, sexual dysfunction, and mood disorders.

5. Limitations of the Evidence

Although the findings are consistent, several methodological weaknesses limit the strength of the conclusions. First, substantial heterogeneity exists in assay techniques, timing of sample collection, and adjustment for confounders such as BMI, diet, and comorbid conditions. Second, many studies relied on small, cross-sectional samples, which precludes causal inference. Third, the underrepresentation of women and lack of long-term follow-up restrict the generalizability of results. Finally, the exclusion of non-English studies may introduce language bias.

6. Future Research Directions

Future studies should prioritize longitudinal designs assessing hormonal recovery after abstinence, include balanced sex representation, and adopt standardized hormonal assays. Investigations into molecular pathways—such as GnRH receptor regulation, opioid receptor polymorphisms, and hepatic enzyme modulation—may provide mechanistic insights. Integrating endocrinology into addiction medicine research could also help personalize interventions, particularly for individuals with persistent hypogonadism or reproductive dysfunction after detoxification.

7. Summary

This review confirms that chronic substance use profoundly alters endocrine homeostasis through both central and peripheral mechanisms. The strongest evidence supports opioid- and alcohol-induced hypogonadism, with cannabis and stimulant effects appearing milder but still clinically relevant. Hormonal suppression contributes to the systemic morbidity observed in addiction and may serve as both a diagnostic marker and therapeutic target in recovery management.

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Implications for Clinical Practice

The findings of this review have several important clinical implications. Chronic substance use is not only a neuropsychiatric condition but also a systemic endocrine disorder that warrants hormonal assessment as part of comprehensive addiction management. Clinicians treating patients with substance use disorders should be aware that symptoms such as decreased libido, menstrual disturbances, infertility, chronic fatigue, or mood instability may indicate underlying hypogonadism or other hormonal abnormalities (Bawor et al., 2015; Brown et al., 2021).

Routine screening of gonadal hormones, including testosterone, estradiol, LH, and FSH, can help identify endocrine dysfunction early. For male opioid or alcohol users presenting with low testosterone, hormone replacement therapy may improve quality of life, energy levels, and treatment adherence, though such interventions must be carefully balanced against relapse risk (Vuong et al., 2010; Daniell, 2002).

In women, addressing menstrual irregularities and hypoestrogenism is vital for reproductive and bone health. Coordination between addiction specialists, endocrinologists, and gynecologists is therefore recommended to ensure an integrated approach. Furthermore, monitoring hormone recovery during abstinence could serve as a biomarker for physiological normalization and relapse prediction.

From a public health perspective, recognizing hormonal disturbances as part of the broader clinical picture of addiction may enhance awareness and reduce stigma. Policies promoting early endocrine evaluation could contribute to improved rehabilitation outcomes and lower relapse rates.

Limitations

Several limitations should be acknowledged when interpreting these findings. First, the majority of studies were cross-sectional, limiting the ability to infer causality between substance use and hormonal alterations. Longitudinal studies examining hormonal recovery after abstinence remain scarce. Second, heterogeneity in hormone measurement techniques, timing of blood sampling, and control for confounding variables (e.g., BMI, nutritional status, or coexisting diseases) introduced variability across results.

Third, there was a clear sex imbalance in available data, with most research focusing on men. Female-specific endocrine outcomes, such as menstrual cycle irregularities or reproductive consequences, were often underreported. Fourth, poly-drug use and coexisting psychiatric or medical comorbidities may have further influenced hormonal outcomes, complicating direct comparisons between substances. Lastly, publication and language biases may exist, as only English-language, peer-reviewed studies were included.

Conclusion

This systematic review demonstrates that substance use disorders significantly disrupt sex hormone balance through central hypothalamic–pituitary suppression and peripheral metabolic mechanisms. The strongest evidence supports opioid- and alcohol-induced hypogonadism, while cannabis and stimulant effects appear less pronounced but still clinically meaningful. These hormonal changes contribute to physical, reproductive, and psychological impairments and may persist even after cessation of substance use.

Routine endocrine evaluation should be integrated into addiction care, particularly for long-term users of opioids or alcohol. Addressing hormonal imbalances may improve rehabilitation outcomes, quality of life, and long-term recovery. Future research should employ longitudinal designs, standardized hormonal assays, and balanced sex representation to further elucidate the dynamics between substance use and endocrine health.

The findings underscore the need for a multidisciplinary model of care that bridges addiction medicine, endocrinology, and mental health services. Recognizing the endocrine consequences of addiction not only enhances clinical management but also supports a holistic understanding of substance use as a disorder affecting the entire human system.

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