SEXUAL MEDICINE REVIEWS REVIEW

# Management Strategies in Opioid Abuse and Sexual Dysfunction: A Review of Opioid-Induced Androgen Deficiency

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ABSTRACT

**Introduction:** Over the last several decades, the opioid epidemic has become a national crisis, largely spurred by the spike in the use of prescription painkillers. With the epidemic came a concomitant rise in the incidence of opioid-induced androgen deficiency (OPIAD). Although OPIAD can significantly impact male sexual function and quality of life, it is an overlooked and poorly understood clinical entity that requires more attention from healthcare providers.

**Aim:** The objectives of the current review are to highlight the increasing incidence of OPIAD and the importance of an integrated, multidisciplinary approach to identify and treat patients with the condition.

**Methods:** This review presents the epidemiology surrounding the current opioid epidemic, with a focus on its origin, followed by a literature review surrounding the pathophysiology, diagnosis, and treatment of OPIAD.

**Main Outcome Measure:** Single-center studies were used to determine the safety and efficacy of various opioid and testosterone formulations on analgesia, sexual function, and quality of life.

**Results:** There should be a low threshold for obtaining laboratory studies (testosterone, luteinizing hormone [LH], follicle-stimulating hormone [FSH]) on symptomatic patients who have a history of chronic opioid use. Treatment options include opioid cessation, short-acting opioids, and testosterone replacement therapy (TRT). The patient and physician should weigh the risks and benefits of TRT against more conservative approaches. Options such as clomiphene and anastrozole are available for patients who wish to preserve fertility.

**Conclusion:** Because OPIAD is an underappreciated and underdiagnosed consequence of chronic opioid abuse, healthcare providers should be particularly vigilant for signs of hypogonadism in this patient population. It is reasonable for pain specialists, urologists, and primary care physicians to closely monitor patients on prescription opioids and discuss available options for treatment of hypogonadism. **Hsieh A, DiGiorgio L, Fakunle M, et al. Management strategies in opioid abuse and sexual dysfunction: A review of opioid-induced androgen deficiency. Sex Med Rev 2018;XX:XXX–XXX.**

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**Key Words:** Opioids; Hypogonadism; Opioid-Induced Androgen Deficiency; Testosterone Replacement Therapy

## INTRODUCTION

U.S. national surveillance mortality data suggests that death caused by heroin abuse has more than quadrupled since 2000, making the current opioid epidemic the worst in U.S. history. Although the overall trend of illicit drug use has decreased in the United States, the incidence of prescription opioid abuse has increased by 81% since the 1990s.[1] Between 2002 and 2013, the number of heroin users has increased from 1.6 to 2.6 per 1,000 persons.[2] During that same time, the heroin overdose death rates in the United States increased from 0.7 to 2.7 deaths per 100,000 persons.[3]

Because of the risk of addiction and possibility of fatal outcomes, the prescription opioid epidemic has grown into a significant healthcare problem affecting the general population.[1] The recent upsurge in opioid use has been accompanied by an increase in the incidence of opioid-induced endocrinopathy, most commonly manifesting as androgen deficiency. Termed opioid-induced androgen deficiency (OPIAD), this condition leads to multiple central and peripheral effects, particularly on sexual function in males. Because of the scale of the opioid epidemic, the concomitant rise in OPIAD, and its effects on the quality of life of patients, the urologic and sexual health communities need to be aware of this condition and how to treat it.

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We present here a review of opioid-induced androgen deficiency, with a discussion of the root of the current epidemic and a focus on the effect of opioids on sexual health.

## BACKGROUND AND EPIDEMIOLOGY

Heroin has historically been associated with lower socioeconomic groups, but the demographics have shifted over the last several decades. Heroin has become far more prevalent in non-urban communities, and the highest increases in heroin use have been in a surprising demographic: non-Hispanic white men. Furthermore, heroin abusers are getting younger, with users aged 18 to 44 having the highest rates of heroin-related deaths at 7.0 per 100,000 persons.[3] In 1 study of the regional and demographic differences in prescription-opioid and heroin-related overdose, heroin overdose rates were noted to be highest in the Midwest and Northeast regions. The study also suggested that new and younger heroin users may be more vulnerable to heroin-related overdoses because of the transition from prescription opioid use to heroin.[2]

The true incidence of OPIAD is difficult to ascertain because symptoms are often non-specific, if present at all. However, small studies have placed the prevalence of OPIAD at 90% in symptomatic men[4] and 53% in asymptomatic men on chronic opioid therapy.[5] These numbers suggest the need for a high index of suspicion in these patients, and providers should use laboratory tests to diagnosis the condition.

## PATHOPHYSIOLOGY OF OPIOID-INDUCED HYPOGONADISM

Opioids exert their analgesic effect through binding and activation of $\mu$-receptors in the presynaptic regions of the periaqueductal gray region, ventromedial hypothalamus, and superficial dorsal horn of the spinal cord. Activation of $\mu$-receptors in other parts of the body produce several well-known side effects, which include dizziness, constipation, urinary retention, nausea, and respiratory depression.[6] Hypogonadism, perhaps the least well-known and investigated effect of chronic opioid use, has been increasingly reported in both men and women chronically taking opioids.

The hypothalamic–pituitary–gonadal axis plays a critical role in the development and regulation of the reproductive system. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner. The pituitary gland responds by releasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate Leydig cells and Sertoli cells, respectively. Fluctuations in the axis cause alterations in sex hormone release, which can have considerable local and system effects. Opioids act on this axis centrally by binding to $\mu$-receptors in the hypothalamus, interrupting the pulsatile release of GnRH and causing downstream effects that limit the production of testosterone, resulting in hypogonadal effects such as decreased libido, erectile dysfunction, and loss of muscle mass.[7]

Opioids act on the hypothalamic–adrenal axis by decreasing dehydroepiandrosterone sulfate (DHEAS) production by the adrenals. Known inhibitors of corticotropin-releasing hormones (CRH), opioids have been reported to lower DHEAS levels in a dose-related pattern, suggesting that decreased CRH may also play in a role in OPIAD.[8] Dehydroepiandrosterone and DHEAS are endogenous precursors to more potent androgens such as testosterone and dihydrotestosterone. Their deficiency can also produce fatigue, depression, weakness, and sexual dysfunction, compounding the symptoms of OPIAD.

Opioids also directly affect the testes. Activation of $\mu$-receptors present on human spermatozoa, predominantly in the plasma membrane of the sperm head and middle tail regions, lead to decreased sperm motility.[9] Studies have shown that opium consumption has significant deleterious effects on semen parameters and sperm chromatin, as measured by the DNA fragmentation index. It has also been demonstrated that chronic opioid users, in comparison to healthy age-matched volunteers, had significantly decreased sperm concentration (22 million vs 66 million/mL), increased DNA fragmentation (36% vs 27%), and significantly decreased levels of catalase-like and superoxide-dismutase activity.[10]

Alosi et al[11] demonstrated a change in the expression of testosterone catabolic enzymes in mice treated with morphine. The study showed that morphine may have long-lasting genomic effects on 5-alpha reductase and P-450 aromatase, increasing their expression in the liver, testes, and brain. In songbirds, testosterone levels and androgen receptor expression in the medial preoptic nucleus increase in the springtime and correlate positively with sexually motivated songs.[12] Cordeset et al[13] demonstrated that opioid release and $\mu$-receptor expression in the same region inhibits sexually motivated songs. These animal models suggest that opioids affect sexual behavior and expression at multiple points, including at the mRNA level.

The literature reports an incidence of hypogonadism ranging between 50% and 90% in chronic opioid abusers.[14] The effect of the opioids on testosterone level has a quick onset and appears to be reversible.[15,16] Rubenstein et al[5] examined 81 men without previous diagnosis of hypogonadism on stable opioid doses for a minimum of 3 months. The incidence of hypogonadism was significantly associated with the duration of action of the opioids (74% vs 34%) but not the total daily dose. The authors proposed that long-acting opioids lead to stable serum opioid levels, which causes more cumulative GnRH suppression in comparison to shorter-acting opioids.

## DIAGNOSIS

There is no definitive guideline for the diagnosis of OPIAD. However, as with other medical conditions, a good first step is obtaining a thorough history. Patients with hypogonadism may complain of increased fatigue, reduced sense of vitality, depressed mood, weight gain, and decreased muscle mass. However, these