



Review

Testosterone suppression in opioid users: A systematic review and meta-analysis[☆]



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ABSTRACT

Background: Whether used for pain management or recreation, opioids have a number of adverse effects including hormonal imbalances. These imbalances have been reported to primarily involve testosterone and affect both males and females to the point of interfering with successful treatment and recovery. We conducted a systematic review and meta-analysis to determine the extent that opioids affect testosterone levels in both men and women, which may be relevant to improved treatment outcomes for opioid dependence and for pain management.

Methods: We searched PubMed, EMBASE, PsycINFO, and CINAHL for relevant articles and included studies that examined testosterone levels in men and women while on opioids. Data collection was completed in duplicate.

Results: Seventeen studies with 2769 participants (800 opioid users and 1969 controls) fulfilled the review inclusion criteria; 10 studies were cross-sectional and seven were cohort studies. Results showed a significant difference in mean testosterone level in men with opioid use compared to controls (MD = −164.78; 95% CI: −245.47, −84.08; $p < 0.0001$). Methadone did not affect testosterone differently than other opioids. Testosterone levels in women were not affected by opioids. Generalizability of results was limited due to high heterogeneity among studies and overall low quality of evidence.

Conclusions: Our findings demonstrated that testosterone level is suppressed in men with regular opioid use regardless of opioid type. We found that opioids affect testosterone levels differently in men than women. This suggests that opioids, including methadone, may have different endocrine disruption mechanisms in men and women, which should be considered when treating opioid dependence.

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1. Introduction

Opioids refer to a class of natural and synthetic drugs that are used for pain management and opioid dependency (Fornasari, 2012). They exert their analgesic effects by binding to opioid receptors in the brain and spinal cord to inhibit neurotransmitter release (Mansour et al., 1987), causing both a reduction in neurotransmission and an inhibition of sensory neurons responsible for pain sensation. However, opioids also act on the respiratory control centers in the brain to cause a reduction in respiratory function, and they promote a reduction in gastrointestinal motility through their action in the digestive tract (Narita et al., 2001; Zhang et al., 2008). When taken appropriately and in recommended dosages, opioids are effective for acute pain relief and management of chronic pain, however they have numerous potential side effects, including sedation, nausea, drowsiness, and constipation (Baumann, 2009). Other side effects include decreases in sexual function, bone deterioration, hair loss, immunodeficiency, and pain sensitivity (Benyamin et al., 2008; Hallinan et al., 2008). Opioids are also known to act on endocrine system function, producing hormonal imbalances that may lead to additional serious adverse effects (Katz and Mazer, 2009).

Testosterone is a sex steroid that is controlled by the hypothalamic–pituitary–gonadal (HPG) axis and produced through a series of hormonal activations, which include the gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). Alterations in testosterone concentration caused by exogenous substances such as opioids can have significant effects on mood, stress reactivity, aggression, and sexual drive (Borjesson et al., 2011; Kosten and Ambrosio, 2002; Smith and Elliott, 2012). It is speculated that chronic opioid use leads to suppression of GnRH, which indirectly lowers production of testosterone (Katz and Mazer, 2009).

In the case of opioid use disorder, testosterone suppression has been documented in opioid-dependent samples (Azizi et al., 1973; Mendelson et al., 1975a, 1975b, 1984; Wang et al., 1978) as well as patients undergoing methadone maintenance treatment (MMT; Bliesener et al., 2005; Cofrancesco et al., 2006; Cushman, 1973). Methadone is a synthetic opioid used to manage opioid use disorder and withdrawal symptoms in substitute opioid therapy (SOT; Mattick et al., 2009). Treatment with methadone incorporates a harm-reduction approach and involves maintaining patients on a stabilized dose of methadone while slowly tapering off, which can

sometimes take years (Mattick et al., 2009). The consequences of testosterone suppression in this particular sample of opioid users may hinder their treatment initiation, maintenance, and recovery.

The incidence of opioid-induced testosterone suppression in women is less commonly examined in the literature. However, a disturbance in female sex hormone levels may also cause the changes that are typically seen in men, and in samples of methadone-treated patients, may lead to poor outcomes and increased risk of relapse.

Based on a review of opioid use and the endocrine system, Katz and Mazer (2009) suggest that all opioids suppress testosterone. Studies on individuals with opioid use disorders, methadone-treated patients, and opioid users for chronic pain alike all showed significant suppression of testosterone. However, the extent of testosterone suppression was not measured quantitatively. A non-systematic narrative literature review showed similar conclusions (Elliott et al., 2011).

Although previous findings support that all opioids suppress testosterone, direct comparisons of testosterone levels among different opioids have not been performed to date. It is possible that some opioids affect testosterone more than others, which would be useful in choosing a particular treatment course. Additionally, having information on testosterone level in opioid users compared to the clinically normal ranges would be helpful for healthcare professionals to determine if this reduction in testosterone is clinically significant and when to initiate treatment of its associated symptoms.

These reviews demonstrate that there is a growing interest in this particular topic as a result of increased rates of opioid use and it is likely that additional studies have been conducted since these reviews were published. There is also a lack of quantifiable data to support the effect of opioids on testosterone, which will be appropriately estimated using a summary statistic derived from a meta-analysis of studies that include small samples. Furthermore, examination of the effect of opioids on testosterone levels in women has yet to be completed, and studies that include samples of women are generally small in this particular area of study, therefore a meta-analysis will provide a larger estimate of effect. The quality of the literature also needs to be evaluated to highlight problematic areas for future research and improvement. Hence, the need for a systematic review with updated data that can be combined statistically in a meta-analysis.

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