LESS IS MORE

Doubts About Treating Hypogonadism Due to Long-term Opioid Use With Testosterone Therapy
A Teachable Moment

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Story From the Front Lines
A man in his 40s with chronic low back pain treated with long-term opioid medication, depression, and hypogonadotrophic hypogonadism was referred to the endocrine clinic by his primary care physician to consider resumption of testosterone therapy. One year prior to presentation, laboratory workup for depression revealed a serum testosterone level of 88 ng/dL (lower limit of normal, 240 ng/dL) (to convert to nanomoles per liter, multiply by 0.0347), serum luteinizing hormone level less than 0.1 mIU/mL (reference range for men aged 30-70 years, 1.5-9.3 mIU/mL) (to convert to international units per liter, multiply by 1.0), serum follicle-stimulating hormone level less than 1.0 mIU/mL (reference range for men aged 30-70 years not defined) (to convert to international units per liter, multiply by 1.0), serum testosterone, follicle-stimulating hormone, luteinizing hormone, and dehydroepiandrosterone. Effects on the HPG and HPA axes can be seen immediately after therapy with opioids is initiated. Current guidelines recommend that the end result of this suppression is decreased levels of testosterone, follicle-stimulating hormone, luteinizing hormone, and dehydroepiandrosterone. Effects on the HPG and HPA axes can be seen immediately after therapy with opioids is initiated. Current guidelines recommend that all patients using more than 100 mg of daily morphine equivalent be monitored for hypogonadism.1 Decreased opioid doses can result in reversal and normalization of testosterone levels as evidenced in a study of heroin addicts.2

Testosterone therapy for hypogonadism is often directed at symptoms related to quality of life including restoration of libido, sexual dysfunction, energy level, and mood. Yet, when these symptoms are studied in patients undergoing testosterone therapy, there is little evidence that use of exogenous testosterone has substantial or meaningful impact on these symptoms.3 When compared with the potential harms of therapy including polycythemia, gynecomastia, acne, sleep apnea, infertility, and decreased bone mineral density, the lack of benefit is troubling.1,4 Furthermore, several recent studies have indicated an increased risk of cardiovascular events with testosterone therapy. Although large placebo-controlled randomized clinical trials are lacking, a 2010 randomized clinical trial examining testosterone use in frail older men was stopped early because of increased cardiovascular adverse events in the treatment group.5 More recently, a large retrospective cohort trial of Veterans Affairs patients aged 60 to 63 years demonstrated that men with testosterone levels less than 300 ng/dL undergoing coronary angiography and subsequently starting testosterone therapy were at significantly greater risk of cardiovascular end points over 3 years compared with men who did not take testosterone: 25.7% vs 19.9% (hazard ratio, 1.29 [95% CI, 1.04-1.58]).6 This information suggests potential and serious harm from testosterone therapy that may outweigh any benefit to quality of life.

Long-term opioid therapy has likely resulted in hypogonadism in this patient, which he believes has negatively affected his ability to enjoy life. The treatment options available are to provide testosterone therapy or to address the underlying cause of his hypogonadism and taper or eliminate his opioid dose. This latter approach would address his underlying endocrine dysfunction, spare him the known risks of high-dose opioids, and prevent any potential harm from exposure to exogenous testosterone. In recognition of the fact that some patients require opioids to manage pain, it may not be feasible to substantially reduce his analgesic dosing. However, without clear and clinically important benefit from testosterone therapy, especially in consideration of the potential serious harm of such therapy, it is difficult to justify its use in this patient.

Teachable Moment
The mechanism by which opioids induce hypogonadism has been well described and consists of suppression of the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes. The end result of this suppression is decreased levels of testosterone, follicle-stimulating hormone, luteinizing hormone, and dehydroepiandrosterone. Effects on the HPG and HPA axes can be seen immediately after therapy with opioids is initiated. Current guidelines recommend that all patients using more than 100 mg of daily morphine
Conflict of Interest Disclosures: None reported.


