

than 14 days of corticosteroid use<sup>3</sup>; thus, administration of steroids should not be delayed while awaiting biopsy.

For our patient, temporal artery biopsy could have been performed as an outpatient procedure, especially given her high risk for developing delirium as an inpatient. Her age, multiple comorbidities, and history of delirium increased her vulnerability to recurrent delirium. A hospital setting exposes patients to polypharmacy, disruption of sleep/wake cycles, and tethers such as intravenous catheters and telemetry, and as many as 11% to 14% of medical patients outside of an intensive care unit develop delirium during their hospitalizations.<sup>4</sup> Delirium leads to longer lengths of stay and higher in-hospital mortality and is associated with an increased rate of death,

institutionalization, and development of dementia.<sup>5</sup> These risks are independent of comorbid illness and baseline dementia, indicating that an episode of delirium itself may have permanent deleterious effects on the brain.

Choosing to hospitalize this patient for a procedure that could have been performed as an outpatient resulted in a prolonged hospital course and the development of delirium, putting her at risk for further adverse outcomes. Hospitalization also inflicted substantial financial burdens and emotional stress on the patient and her family. This case should prompt physicians to consider the risks of hospitalization carefully when deciding on the best setting for a patient's workup or procedure.

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## PERSPECTIVE

## 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 hypogonadotropic 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). Testosterone therapy by injection was initiated and continued for 6 months with reported improvement of depressive symptoms, although he did experience occasional mood swings. After 6 months of testosterone therapy, the patient experienced urinary retention and therapy was discontinued. After urologic consultation, it was determined that his lower urinary tract symptoms were most likely due to opioid medication use rather than prostatic enlargement. Discussion with his

primary care physician included attempts to taper his opioid medication use, but he was still referred for management of his hypogonadism. In the endocrine clinic, he described a long history of fatigue, decreased libido, erectile dysfunction, and insomnia. After a detailed discussion of potential benefits and risks, he expressed a strong desire to resume testosterone therapy given his former perceived improvement in mood. Repeated laboratory evaluation reaffirmed hypogonadotropic hypogonadism without other pituitary dysfunction. He was prescribed testosterone gel rather than injections in an attempt to mitigate his mood swings.

### 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 equivalent be monitored for

hypogonadism.<sup>1</sup> Decreased opioid doses can result in reversal and normalization of testosterone levels as evidenced in a study of heroin addicts.<sup>2</sup>

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.<sup>3</sup> 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.<sup>1,4</sup> 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.<sup>5</sup> 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]).<sup>6</sup> 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.

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