

## FAST FACTS AND CONCEPTS #284 OPIOID-INDUCED ANDROGEN DEFICIENCY

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**Introduction** Opioid-induced androgen deficiency (OPIAD) is a common, yet under-diagnosed consequence of prolonged opioid therapy; this *Fast Fact* will review OPIAD.

**Demographics** Biochemical and clinical hypogonadism have been observed in patients receiving intrathecal, transdermal, and sustained-release opioids [1]. Hypothalamic-pituitary-gonadal axis (HPA) suppression has been demonstrated within hours of methadone exposure, but risk appears to increase with increasing doses for extended durations. Some studies have found a dose-response effect with increased testosterone suppression at higher opioid doses [2, 3]. As many as 50-100% of patients receiving daily opioid doses equivalent to 100-200 mg oral morphine for more than one month will have some degree of OPIAD [4, 5]. In one observational study, 89% had biochemical evidence of hypogonadism, and 87% reported severe erectile dysfunction or diminished libido after starting opioids despite normal erectile dysfunction before using opioids [6]. One study found that men may have higher prevalence of hypogonadism than women [7]. Teenage patients have not been studied.

**Physiology** OPIAD results primarily from suppression of the HPA and is a form of secondary (hypogonadotropic) hypogonadism. Opioids inhibit secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus, leading to decreased sex hormone secretion [4, 5]. Opioids may also decrease adrenal androgen synthesis and directly inhibit testicular testosterone synthesis [4, 6].

**Symptoms and Signs** Hypogonadism can cause decreased libido, erectile dysfunction, decreased fertility, fatigue, irregular menstrual cycle, weight gain, depression, osteoporosis, or hot flashes [4, 5]. Physical findings include decreased facial and body hair, reduced muscle mass, increased body fat, and small or shrinking testes [5, 8].

**Diagnosis** Because the incidence is high and data about dosing thresholds is unknown, OPIAD should be considered in any patient on opioids with signs or symptoms of hypogonadism [5]. Measurable improvements in depressed mood and energy have been documented after 12 weeks of testosterone therapy [9, 10]. However, many of the symptoms of OPIAD are also caused by advanced illnesses, making it difficult to attribute them appropriately. There are no data to guide decision-making about OPIAD in advanced illness. It is reasonable to limit clinical evaluation of OPIAD to patients whose prognoses are judged to be sufficiently long enough to benefit from OPIAD treatment [9].

- **Men:** Test the total serum testosterone drawn at 8 am (normal range in most laboratories is 300 to 800 ng/dl). If abnormal or borderline, repeat the test at 8 am once more (as levels may fluctuate day to day). Obesity and older age reduce hormone binding proteins and can interfere with results. Additional confirmatory testing can include free testosterone, serum hormone binding globulin, LH, FSH, and prolactin. [4, 8] Men with diagnostic uncertainty should be seen by an endocrinologist.
- **Women:** There are currently no established diagnostic criteria in women. Women with symptoms of OPIAD should be referred to an endocrinologist.

**Management** There is no direct evidence as to whether OPIAD improves with opioid rotation or dose reduction (short of cessation). Since improvement of other opioid side effects vary among patients with opioid rotation or dose reduction, these may be attempted [2]. If this is unsuccessful, hormone replacement may be considered.

**Testosterone Replacement** Cessation of opioid therapy can lead to recovery of normal serum testosterone levels within days of discontinuation [5]. Testosterone replacement therapy for women is not FDA approved, but may be appropriate for some patients [5, 11]. Management of OPIAD in women who need to remain on opioid therapy is not established and is best managed by an endocrinologist. For men who need to remain on opioid therapy, testosterone replacement is the mainstay. It may be administered by intramuscular injections, buccal tablets, or transdermal patches, gels, or creams [4, 5]. Doses and frequencies vary by route and dosage form.

- **Precautions:** Testosterone treatment is not recommended in patients with breast or prostate cancer, a palpable prostate nodule, or PSA greater than 4 ng/ml or greater than 3 ng/ml in patients at high risk for prostate cancer [8].
- **Adverse Effects:** Increased hemoglobin and hematocrit, decreased HDL, hypoglycemia, hypercalcemia, edema, acne, gynecomastia, headache, mood swings, BPH. Recent retrospective studies [12, 13] have found an association between testosterone therapy and increased mortality, MI, and stroke. These studies are controversial and prospective data is needed. The FDA also recently added a warning about potential risk of venous blood clots unrelated to polycythemia [14].
- **Monitoring:** Effects of testosterone therapy typically occur within the first three to six months of treatment [9]. Therefore, serum testosterone levels should be measured 3-6 months after starting testosterone therapy and then annually.
  - Measure the level midway between injections in men receiving IM injections. The total testosterone level should be in the mid-normal range, 400-700 ng/dL [8].
  - Practice guidelines recommend men age 40 and older who have baseline PSA>0.6 ng/ml should have DRE and PSA measurement before initiating therapy, at 3-6 months, then in accordance with normal screening guidelines. Urological consultation is recommended if there is an increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment [8].
  - Hematocrit should be measured before starting therapy, after three to six months, and then yearly to screen for erythrocytosis [8].

**Conclusion** OPIAD is an under-diagnosed consequence of prolonged opioid therapy, and untreated patients may have reduced quality of life [5]. Men who are diagnosed with OPIAD may be treated with testosterone therapy with appropriate monitoring. Diagnosis and treatment of OPIAD in women is not well established and should be referred to an endocrinologist.

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