Opioids and the Hypothalamic-Pituitary-Gonadal (HPG) Axis

Leen Wehbeh[1] and Adrian S. Dobs[1]

[1]Division of Endocrinology, Diabetes & Metabolism, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21287

ORCiD numbers: 0000-0001-6045-0706 (L. Wehbeh); 0000-0003-1041-6061 (A. S. Dobs).

Context: Hypogonadism is a well-established consequence of opioid use. It has been reported in both men and women, although more widely studied in men.

Evidence Acquisition: PubMed was searched for articles in English until December 2019 for opioids and hypogonadism. Bibliography of retrieved articles was searched for relevant articles.

Evidence Synthesis: The prevalence of opioid-induced hypogonadism (OIH) varies between studies but was reported to be 69% in a recent systematic review. There is large heterogeneity in the studies, with different factors shown to have stronger association with hypogonadism such as specific types of opioids, higher doses, and longer durations of use. The consequences of OIH include sexual dysfunction, depression, decreased quality of life, and low bone density. There is paucity of randomized controlled trials assessing the efficacy of testosterone replacement therapy (TRT) for OIH in men, and even less studies on treating OIH in women. TRT studies in men reported varying outcomes with some studies favoring and others showing no clear benefit of TRT on different measures.

Conclusions: Despite the high prevalence of OIH, it remains underrecognized and undertreated with multiple endocrine and metabolic consequences. A reasonable approach in patients using opioids includes informing them of this complication and its potential consequences, screening for signs and symptoms of hypogonadism then sex hormone levels if prolonged opioid use > 3 months, and treating patients diagnosed with hypogonadism, if and when clinically indicated, with sex hormones if chronic opioids are planned to be continued for ≥ 6 months. **(*J Clin Endocrinol Metab* 105: 1–9, 2020)**

Freeform/Key Words: estradiol, hypogonadism, opioids, testosterone

Introduction

The United States has been facing an opioid epidemic that was precipitated by increasing number of opioid prescriptions by more than 300% between 1999 and 2010(1). This later led to awareness of the opioid problem and efforts to reduce the unnecessary prescribing of opioids with resultant increase in the illicit use of heroin as an initiating drug for opioid addiction (2). In 2018, the Centers for Disease Control and Prevention (CDC) estimated the number of people with opioid use disorder at 2 million (3), with more than 130 people dying every day from opioid-related drug overdose. In addition to the devastating risks of opioid addiction, there are many less serious chronic side effects of opioid use, even when taken as directed including constipation, nausea, vomiting, dry mouth, somnolence, depression, and endocrine disorders. Hypogonadism is the most common endocrine side effect of opioid use

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Abbreviations: BMD, bone mineral density; BUP, buprenorphine; CDC, Centers for Disease Control and Prevention; CI, confidence interval; DHEA-S, dehydroepiandrosterone sulfate; E2, estradiol; HPG, hypothalamic-pituitary-gonadal; HR, hazard ratio; METH, methadone; OR, odds ratio; RCT, randomized clinical trial; T, testosterone; TRT, testosterone replacement therapy.

and is the focus of the current review. We, as endocrinologists, are often consulted to evaluate hypogonadism and we should be able to assess, diagnose, and treat opioid induced hypogonadism if clinically indicated.

Opioid Effects on the Hypothalamic-Pituitary-Gonadal Axis

The effects of opioids on the hypothalamic-pituitary-gonadal (HPG) axis have been reported in the literature since the 1970s, with multiple studies showing evidence of low testosterone (T) in opioid users 4-6), and other studies showing an association between long-term opioid use and prescriptions for erectile dysfunction or T replacement, especially when the morphine equivalent daily dose was > 120 mg (7).

Opioid effects on the HPG axis in men

The majority of studies evaluating T levels in men have shown T suppression in opioid users in comparison with control groups or normal reference ranges. The prevalence of hypogonadism in different studies ranged between 28% and 86% of men using opioids for different indications (analgesia, illicit use, or opioid substitution therapy to treat opioid addiction) (4, 8-16). A recent systematic review and meta-analysis by De-Vries et al in 2019 evaluated 15 studies with 3250 subjects (99.5% males) using opioids for chronic pain or maintenance treatment for opioid addiction, with methadone being the most frequently used opioid, reported a prevalence of 63% (95% confidence interval [CI], 55-70). The prevalence was 69% (95% CI, 50-85) when the authors evaluated the only 7 studies with low risk of bias (17).

Many studies have shown that T levels in men using different types of opioids were significantly lower than controls. A systematic review and meta-analysis in 2015 by Bawor et al (18) examined the effect of opioids on T levels in men. The analysis included 17 studies (10 cross-sectional and 7 cohort studies, 6 studies on methadone and 11 on opioids excluding methadone), with total number of 607 opioid users and 1417 controls. The mean T levels in the opioid users ranged between 100 and 577 ng/dL (3.47-21.18 nmol/L) compared with a range between 287 and 700 (9.95-24.27 nmol/L) in the controls in all 17 studies. T values were significantly lower in opioid users compared with controls (mean difference = -164.78 ng/dL [-5.71 nmol/L]; 95% CI, -245.47 to -84.08 ng/dL [-8.51 to -2.92 nmol/L]; $P < 0.0001$) with no difference in T levels between methadone and other types of opioids. Some studies in this systematic review and meta-analysis did not control for important potential confounders like opioid dose, opioid duration, body mass index and other factors, and the overall quality of evidence for this study was low.

The different prevalence of hypogonadism in different studies could be related to heterogeneity in evaluating different types of opioids and patient characteristics (chronic cancer pain, chronic non-cancer pain, illicit opioid use, and opioid substitution therapy), and variations in the definition of hypogonadism, which was mostly only based on biochemical and not clinical evaluation, and assessing either total and/or free T levels using different assays and cutoff levels for diagnosis. Moreover, most studies did not have confirmatory testing for the diagnosis of hypogonadism with repeat morning measurement of T as suggested by the Endocrine Society Guidelines (19). However, this is not uncommon in research settings given the added time and cost associated with it.

Another consideration is age. Opioids were found to be associated with low T in different studies evaluating opioid using men across all age groups (10, 20). However, it is expected to see more pronounced effect of opioids on lowering T levels in opioid using men of older age because increasing age and number of comorbidities are known to be associated with male hypogonadism. This was indeed illustrated in a cross-sectional study using 2011-2012 National Health and Nutrition Examination Study by Cepeda et al (21), where they reported that participants > 70 years of age had higher odds of low T compared with participants between 17 and 45 years of age after controlling for opioid use (odds ratio [OR], 1.7; 95% CI, 1.16-2.5). Another retrospective study from Kaiser database found that age > 50 years plus the presence of ≥ 2 comorbidities (diabetes, hypertension, and hyperlipidemia) was a significant contributor to androgen deficiency in opioid using males (22).

Opioid effects on the HPG axis in women

Assessing HPG dysfunction in females is less straight forward than in males, and is rarely done with a simple blood test. Significant differences in terms of amenorrhea and menstrual irregularities were shown in one study occurring in 19% and 50%, respectively, of 16 premenopausal women on chronic oral or spinal morphine for non-cancer pain (23). Increased risk of menopause (hazard ratio [HR], 1.13; 95% CI, 1.05-1.21) and altered menstruation (HR, 1.16; 95% CI, 1,10-1.23) was shown in a matched cohort study in the United Kingdom looking at 44,260 women on chronic opioids for musculoskeletal pain (24). Another case-control study of intrathecal opioids showed that all 21 premenopausal women in that study had amenorrhea

or menstrual irregularities with ovulation occurring only in 1 woman, and all 18 postmenopausal women had significantly decreased LH ($P < 0.001$) and FSH ($P = 0.012$) levels (15). Estradiol (E2) levels were also evaluated in some studies as another indicator of HPG dysfunction in females, and they were found to be significantly lower in 16 premenopausal women treated with oral opioids compared with controls but not in the 8 postmenopausal women in that study (9). A study by Daniell (16) on 47 women using oral or transdermal opioids for chronic noncancer pain showed that T, E2, and dehydroepiandrosterone sulfate (DHEA-S) levels were 48% to 57% lower in opioid users compared with controls in premenopausal women. However, E2 levels were not statistically significantly different in postmenopausal women when comparing opioid users with controls, which is to be expected as the ovaries seize to make E2 postmenopause and suppressing FSH/LH as a result of opioids might not cause the same effect on lowering E2 production. LH and FSH levels were averaged 30% and 70% lower in premenopausal and postmenopausal women, respectively, in that study.

The effects of opioids on T levels in women were reported with conflicting results in different studies, with suppressed T in opioid-using women demonstrated in some studies (12, 16, 25), but not in others 26-29). The same systematic review and meta-analysis by Bawor et al (18) assessed the effect of opioids on T levels in women in 2 studies only (16, 26), and did not find a significant difference (mean difference, -6.17 ng/dL [-0.21 nmol/L]; 95% CI, -39.87 to 27.54 ng/dL [-1.38 to 0.95 nmol/L]; $P = 0.72$).

These findings support the notion of suppression or dysfunction of the HPG axis with chronic opioid use even in women, using measures other than T levels. DHEA-S levels were also found to be significantly lower in opioid-using women in multiple studies (12, 16, 23, 28), although this effect is not directly linked to the HPG axis but rather the hypothalamic-pituitary-adrenal axis because DHEA-S is the main androgen hormone in females coming from the adrenal gland and is under the regulation of ACTH.

Mechanism of Opioid Effects on the HPG Axis

It is thought that the HPG axis is under tonic inhibitory effect of endogenous opioids (30) (Figure 1). Opioids cause suppression of the HPG axis by downregulating GnRH mRNA levels leading to decreased secretion of GnRH from the hypothalamus (30). They also reduce pituitary response to GnRH, consequently causing

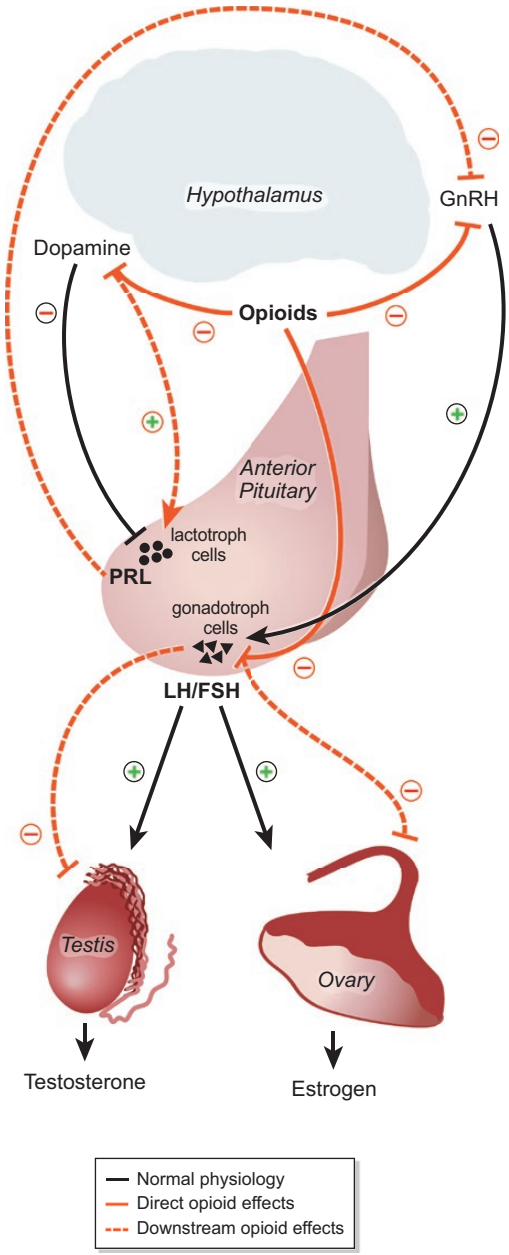

Figure 1. Mechanism of opioid effects on the HPG axis. Opioids suppress hypothalamic GnRH leading to suppression of pituitary LH (and FSH to a lesser degree), which in turn leads to decreased sex hormone production from the gonads (testosterone and estradiol from the testes and ovaries, respectively). Opioids also cause suppression of dopaminergic pathway, leading to hyperprolactinemia which also suppress pituitary LH and eventually lead to decreased sex hormone production from the gonads. GnRH, gonadotropin-releasing hormone; PRL, prolactin.

reduced LH and, to a lesser degree, FSH secretion from the anterior pituitary, which in turn leads to decreased secretion of T from the testes in men and E2 from the ovaries in women, resulting in hypogonadism in both men and women. Injection of the endogenous opioid ß-endorphin (that mainly acts on the mu opioid receptor) IV into distinct hypothalamic areas in ovariectomized rats was found to decrease LH

secretion (31). Furthermore, antagonizing the opioid receptors with naloxone or naltrexone was found to increase GnRH and LH secretion. These findings support the notion that the opioid effects on the HPG axis occur at the level of the hypothalamus and suggest that these effects could be mediated by the mu receptor. However, other receptors, like the epsilon opioid receptor, was thought to be implicated as well (32). Another hypothesis is that chronic stimulation of the mu opioid receptors causes alteration of dopaminergic pathways, with reduced dopamine secretion and the resultant disinhibition of prolactin secretion and subsequent inhibition of GnRH (30).

In animals, the role of mu opioid receptor was studied in sexually motivated song in male starling birds and it was found that low-singing male starlings had denser mu opioid receptor in the hypothalamic preoptic nucleus, and blocking these mu receptors caused increased song bout and rate (33).

Treatments of Opioid Dependence and Their Effects on the HPG Axis

Chronic management of opioid addiction utilizes opioid substitution therapy. Long-term use of methadone (METH) and buprenorphine (BUP) are commonly used treatments. METH is a strong mu opioid receptor agonist, whereas BUP is a partial mu receptor agonist.

Most studies evaluating the effect of METH on the HPG axis showed positive association with hypogonadism and lower T in a dose-related pattern (26, 34, 35). However, a study on HIV-infected men did not concur with this and found no significant association between METH and low T in multivariable analyses after adjusting for different factors (36).

Some studies compared the effect of METH with that of BUP on the HPG axis, trying to delineate superiority of BUP to METH in terms of hypogonadism. One of the first studies to show that BUP, in contrast to high-dose METH, seemed not to suppress plasma T levels in heroin addicts was conducted in 2005 by Bliesener et al (13) and compared 17 patients on sublingual BUP (dose, 11.2 ± 4.3 mg/d; range, 8-20 mg/d) to 37 patients on oral METH (dose 88.4 ± 16 mg/d; range, 60-120 mg/d) and 51 healthy controls. They demonstrated that BUP group had significantly higher T levels and significantly lower frequency of sexual dysfunction compared with METH with no significant difference in T levels between BUP and control groups. By closely observing the mean doses of both medications in this study, and considering a morphine milligram equivalent conversion factor of 30 for sublingual BUP and 12 for METH (at a dose > 80 mg/d) based on the CDC data from 2016 (37), it is noted that the mean morphine milligram equivalent dose for METH group is much higher compared with the BUP group (1060 vs 336 mg/d), which could explain the difference in the effect on the HPG axis between the 2 groups. The difference in dosing was present in the other few studies comparing the 2 medications as well (38, 39). It is possible that BUP doses are lower than METH doses because of the characteristic of "ceiling effect" of BUP (40); that is, being a partial agonist of the mu opioid receptor, higher doses would not produce more effect after a certain point and BUP is sometimes given in flexible doses adjusted to participant need. This is in contrast to METH, the strong mu opioid receptor agonist, with higher doses causing more analgesia and euphoria described as a "high" (40), making patients request higher doses to get this euphoric effect. Although BUP was also linked to hypogonadism, the prevalence was lower than with METH at 23% vs 41% in 1 study (39), and 28% vs 65% in another (8). This latter study had significantly longer duration of opioid substitution therapy in the METH group compared with BUP group, which might have also contributed to the variation in HPG suppression with the assumption that longer duration of use would cause more pronounced suppression. Last, METH is typically used for severe opioid dependence because it was shown to be more effective in retaining patients in treatment programs and suppressing illicit opioid use compared with BUP, which is typically used for mild or moderate dependence (40, 41). Thus, the hypogonadism noted could reflect the severity and duration of opioid use preceding opioid substitution therapy. In a meta-analysis of 4 studies, Yee et al (42) reported higher odds of sexual dysfunction in METH compared with BUP, and they identified 9 factors contributing to sexual dysfunction in opioid users, namely age, hormonal assays (T and E2 levels), duration of opioid substitution therapy, METH dose, medical status, psychiatric illness, other current substance use, familial status, and METH vs BUP treatment. However, this meta-analysis suffered from methodological limitations.

METH use has also been linked to sexual dysfunction independent of the T levels and hypogonadism in 2 studies, suggesting that other factors like childhood adversities and comorbid psychiatric symptoms in METH users might also contribute to sexual dysfunction (35, 43). A recent phase 2, double-blind, parallel-group, placebo-controlled trial by Yee et al (44) in 2018 on 80 METH patients randomized to bupropion (dopamine reuptake inhibitor) or placebo, demonstrated improvement in measures of total T levels and sexual

function in the bupropion arm compared with placebo at the end of study (6 weeks). It is possible that the observed improvement in sexual function is a direct effect of improvement in the T levels in the bupropion group, and this could be promising to alleviate the sexual dysfunction associated with METH use and possibly improve compliance and retention to opioid substitution therapy because it has been suggested by Hallinan et al (38) that sexual dysfunction associated with METH use increased the risk of dropout from METH maintenance therapy prematurely.

From the perspective of hypogonadism as a side effect of opioid use, BUP seems more appealing compared with METH because sexual dysfunction and hypogonadism are important undesired side effects that could pose a barrier to compliance from a patient perspective. However, BUP is more expensive, less effective, and used only for mild or moderate dependence, which might make it less preferred in certain situations (40).

Heterogeneity of Studies Assessing Opioid Effects on the HPG Axis

The variation in opioid effects on the HPG axis is due in part to the type, dose, and duration of action of the opioid used. A study by Rubinstein et al (11) retrospectively evaluated 1585 men on stable chronic opioids from a Kaiser database and demonstrated that long-acting opioids were more likely to cause hypogonadism compared with short-acting opioids (57% vs 35%, $P < 0.001$; OR 3.39; 95% CI, 2.39,4.77). This was thought to be due to having more opioid drug level nadir in the short-acting opioids which allow T production whereas the long-acting opioids were thought to have more stable serum drug level and continued suppression of the HPG axis. There was also strong association between the dose of opioid and hypogonadism in this study although this association seemed to be stronger for short-acting opioids rather than long-acting ones. The inverse relationship between T levels and opioid dose was also shown in some studies (11, 20, 26, 45, 46), but not in others (10, 35).

The same Kaiser group also evaluated 1,159 men on stable chronic opioids and demonstrated that fentanyl, METH, and oxycodone were more likely to cause hypogonadism compared with hydrocodone, with OR of 25.7 (95% CI, 2.82-234.97), 7.33 (95% CI, 3.29-16.33), and 3.15 (95% CI, 1.87-5.33), respectively (22). The authors concluded that the highest odds of hypogonadism were observed with opioids that were able to maintain the most constant serum drug levels and thus not allowing any T production.

There could also be heterogeneity related to the type of opioid receptor. Different opioids work on different receptors, and these receptors have different distributions in the body; this could account for some of the variation.

Treatment of Opioid-Induced Hypogonadism in Men

Hypogonadism in men is associated with a wide range of consequences, including decreased libido, sexual dysfunction (9), decreased quality of life (9), depression (47), low bone mineral density (BMD) (48, 49), decreased muscle mass, and increased fat mass (50).

Multiple studies evaluated T replacement therapy (TRT) in opioid-induced hypogonadism and its outcomes on different measures with varying results. A systematic review by AminiLari et al (51) in 2019 reviewed 5 studies (1 randomized controlled trial [RCT] and 4 observational studies) that looked at TRT for opioid-induced hypogonadism in chronic non-cancer pain and reported improvement in pain and emotional functioning based on very low-quality evidence. However, they found that TRT had no effect on sleep quality, sexual function, physical functioning, role functioning, or social function based on low-quality evidence and no effect on depressive symptoms based on very low-quality evidence. The RCT in this systematic review was conducted in 2015 by Basaria et al (52) and studied TRT efficacy on pain as a primary outcome and reported improved hyperalgesia (pressure and mechanical) and sexual desire in the TRT group compared with placebo. The same group, in different studies on the same cohort, reported no improvement in pain catastrophizing or sleep quality (53), and no worsening of inflammatory or metabolic markers (54). Interestingly, the systematic review reported, with low-quality evidence, no improvement in sexual function based only on evaluating the RCT by Basaria et al (52) although 3 other studies did report improved sexual function with TRT 55-57). However, it is important to note that some studies showed negative association between T levels in opioid users and symptoms of sexual dysfunction (12, 43). A study by Brown et al (43) reported a prevalence of sexual dysfunction in methadone using men of 14%, which the authors thought was a similar rate compared with the general population and failed to show an association between plasma T levels and sexual dysfunction parameters. Similarly, a study by Wong et al (12)

showed similar rates of sexual dysfunction in men and women on opioids and a control group with no association between sex hormone levels and sexual dysfunction symptoms. This underscores the occasional lack of association between low T levels and symptoms of sexual dysfunction, and the need to consider other comorbidities as contributors to these symptoms. This was also shown by a large population study on late-onset hypogonadism by Wu et al (58) that reported a high prevalence (25%) of symptoms of sexual dysfunction even with unequivocally normal T levels and vice versa. Depression scores were also shown to be improved with TRT in some studies (47, 55, 56), despite the lack of improvement reported in the systematic review.

In terms of opioid requirements, a retrospective study reported a decrease in opioid requirements in addition to improvement in pain parameters in the TRT group compared with the no-TRT group (59). The effect of TRT on bone was not evaluated in the previously discussed systematic review, but this was studied by Finch et al (49) in an observational study on 27 men receiving intrathecal opioids (11 on TRT and 16 not on TRT), and they reported significantly higher prevalence of low T and low bone density in the no-TRT group compared with TRT group (87% and 69% vs 18% and 27%, respectively), with significant association documented between low free T levels and low BMD scores. Multiple studies reported a higher prevalence of low BMD in opioid-using men compared with women (23, 34, 60, 61), which suggests sex differences in the opioid effects on bone.

The systematic review did not explore studies addressing the effect of opioid withdrawal on T levels, but an older study in 1974 by Mendelson and Mello (6) showed improving T levels starting one month after opioid (heroin) withdrawal, which is mechanistically expected as lifting the suppression from the HPG axis should result in resumption of normal signaling and function of the HPG axis.

A recent large cohort study from the Veterans Health Administration system by Jasuja et al (62) evaluated the health outcomes of TRT for opioid-induced hypogonadism in men. They compared 14,121 men with opioid-induced hypogonadism who were prescribed TRT with 7151 men with opioid-induced hypogonadism who did not receive TRT and reported significantly lower all-cause mortality (HR, 0.51; 95% CI, 0.42-0.61), lower incidence of major adverse cardiovascular events (HR, 0.58; 95% CI, 0.51-0.67), femoral or hip fractures (HR, 0.68; 95% CI, 0.48-0.96), and anemia (HR, 0.73; 95% CI, 0.68-0.79) during a 6-year follow up period in the TRT group compared with the no-TRT group. This study strongly suggests benefit of using TRT for opioid-induced hypogonadism on multiple health outcomes; however, it is an observational cohort study that warrants further confirmation with RCT.

Last, a recent commercial insurance database study by Baillargeon et al (63) on 53,888 men on opioids for more than 90 days and 53,888 matched controls (<14 days of opioid use) did indeed report that opioid users compared with controls had an increase in each of the following measures: screening with T levels (17% vs 12%), diagnosing hypogonadism (9% vs 5%), and receipt of TRT for hypogonadism (6% vs 2%), but it is evident that these rates are much lower than expected based on the large body of literature, suggesting higher prevalence of opioid-induced hypogonadism.

Conclusion

Opioid-induced hypogonadism is a well-established problem during the opioid epidemic, with a high prevalence of 69% reported based on a recent systematic review and meta-analysis (17). The prevalence in the literature varies widely depending on multiple factors, such as the definition of hypogonadism, type and duration of action of opioid, and dose, indication, and duration of opioid use. Opioid-induced hypogonadism has multiple endocrine and metabolic consequences including reduced quality of life, sexual dysfunction, and low BMD. However, there is paucity of RCTs assessing the efficacy of TRT in male opioid-induced hypogonadism and there are even fewer studies on treating opioid-induced hypogonadism in women. The studies evaluating TRT in men are mostly observational, with conflicting results. We need more RCTs to better inform our treatment decisions and assess the benefits of TRT in this population. Despite our lack of understanding of the effects of TRT on opioid-induced hypogonadism in men, it might be reasonable to consider treatment to improve bone health and possibly sexual dysfunction symptoms because the discontinuation or at least dose reduction of opioids is not always feasible. Given the lack of recognition of this condition, it is important for endocrinologists to recognize, screen for, diagnose, and treat this condition, in the absence of contraindications, to possibly improve patient outcomes. A reasonable approach is outlined in Figure 2 and would include informing all patients on opioids or planned to start prolonged opioid treatment of this complication to the gonadal axis and its potential consequence, screening all

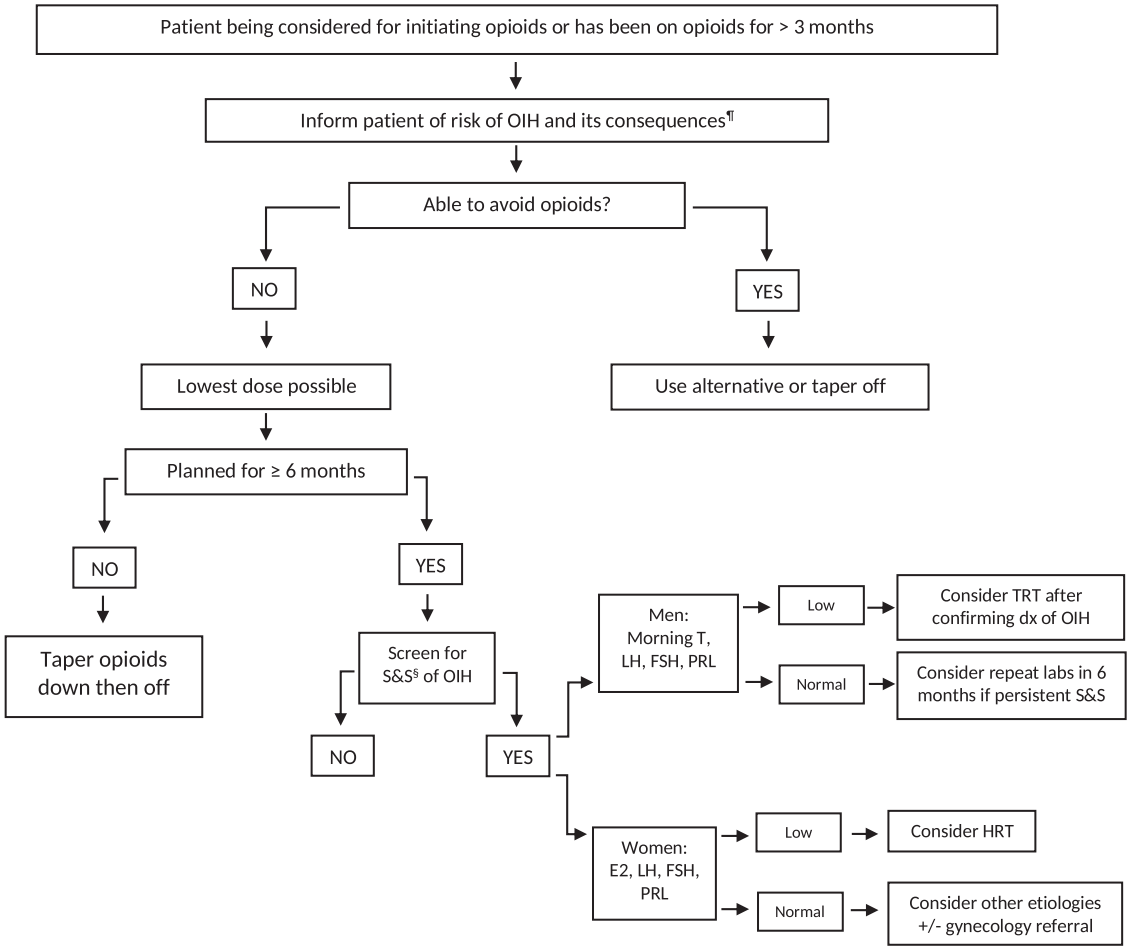

Figure 2. Suggested algorithm for evaluation and management of opioid-induced hypogonadism (OIH). Reduced sexual function, reduced QoL, depression, decreased BMD, decreased muscle mass, increased fat mass. §Men: decreased libido, decreased erections, depression, anemia, decreased muscle mass/strength; women: amenorrhea, menstrual irregularities. Abbreviations: E2, estradiol; HRT, hormonal replacement therapy; PRL, prolactin; S&S, signs and symptoms; T, testosterone; TRT, testosterone replacement therapy.

patients on chronic opioids for more than 3 months for signs and symptoms of hypogonadism and sex hormone levels if present, and treating patients diagnosed with hypogonadism, if clinically indicated, with sex hormones if chronic opioids are planned to be continued for at least 6 months.

Additional Information

Correspondence: Leen Wehbeh, MD, Division of Endocrinology, Diabetes & Metabolism, The Johns Hopkins University School of Medicine, 1830 E. Monument Street, Suite 333, Baltimore, MD 21287. E-mail: lwehbeh1@jhmi.edu

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