SEXUAL MEDICINE REVIEWS REVIEW

Management Strategies in Opioid Abuse and Sexual Dysfunction: A Review of Opioid-Induced Androgen Deficiency

Alan Hsieh, BA,[1] Lorenzo DiGiorgio, MD,[1] Mary Fakunle, BA,[1] and Hossein Sadeghi-Nejad, MD[1,2]

ABSTRACT

Introduction: Over the last several decades, the opioid epidemic has become a national crisis, largely spurred by the spike in the use of prescription painkillers. With the epidemic came a concomitant rise in the incidence of opioid-induced androgen deficiency (OPIAD). Although OPIAD can significantly impact male sexual function and quality of life, it is an overlooked and poorly understood clinical entity that requires more attention from healthcare providers.

Aim: The objectives of the current review are to highlight the increasing incidence of OPIAD and the importance of an integrated, multidisciplinary approach to identify and treat patients with the condition.

Methods: This review presents the epidemiology surrounding the current opioid epidemic, with a focus on its origin, followed by a literature review surrounding the pathophysiology, diagnosis, and treatment of OPIAD.

Main Outcome Measure: Single-center studies were used to determine the safety and efficacy of various opioid and testosterone formulations on analgesia, sexual function, and quality of life.

Results: There should be a low threshold for obtaining laboratory studies (testosterone, luteinizing hormone [LH], follicle-stimulating hormone [FSH]) on symptomatic patients who have a history of chronic opioid use. Treatment options include opioid cessation, short-acting opioids, and testosterone replacement therapy (TRT). The patient and physician should weigh the risks and benefits of TRT against more conservative approaches. Options such as clomiphene and anastrozole are available for patients who wish to preserve fertility.

Conclusion: Because OPIAD is an underappreciated and underdiagnosed consequence of chronic opioid abuse, healthcare providers should be particularly vigilant for signs of hypogonadism in this patient population. It is reasonable for pain specialists, urologists, and primary care physicians to closely monitor patients on prescription opioids and discuss available options for treatment of hypogonadism. **Hsieh A, DiGiorgio L, Fakunle M, et al. Management strategies in opioid abuse and sexual dysfunction: A review of opioid-induced androgen deficiency. Sex Med Rev 2018;XX:XXX–XXX.**

Published by Elsevier Inc. on behalf of the International Society for Sexual Medicine.

Key Words: Opioids; Hypogonadism; Opioid-Induced Androgen Deficiency; Testosterone Replacement Therapy

INTRODUCTION

U.S. national surveillance mortality data suggests that death caused by heroin abuse has more than quadrupled since 2000, making the current opioid epidemic the worst in U.S. history. Although the overall trend of illicit drug use has decreased in the United States, the incidence of prescription opioid abuse has increased by 81% since the 1990s.[1] Between 2002 and 2013, the number of heroin users has increased from 1.6 to 2.6 per 1,000 persons.[2] During that same time, the heroin overdose death rates in the United States increased from 0.7 to 2.7 deaths per 100,000 persons.[3]

Because of the risk of addiction and possibility of fatal outcomes, the prescription opioid epidemic has grown into a significant healthcare problem affecting the general population.[1] The recent upsurge in opioid use has been accompanied by an increase in the incidence of opioid-induced endocrinopathy, most commonly manifesting as androgen deficiency. Termed opioid-induced androgen deficiency (OPIAD), this condition leads to multiple central and peripheral effects, particularly on sexual function in males. Because of the scale of the opioid epidemic, the concomitant rise in OPIAD, and its effects on the quality of life of patients, the urologic and sexual health communities need to be aware of this condition and how to treat it.

Received November 5, 2017. Accepted April 27, 2018.

[1]Division of Urology, Department of Surgery, Rutgers New Jersey Medical School, Newark, NJ, USA;

[2]Department of Urology, Hackensack University Medical Center, Hackensack, NJ, USA

Published by Elsevier Inc. on behalf of the International Society for Sexual Medicine.
https://doi.org/10.1016/j.sxmr.2018.04.003

We present here a review of opioid-induced androgen deficiency, with a discussion of the root of the current epidemic and a focus on the effect of opioids on sexual health.

BACKGROUND AND EPIDEMIOLOGY

Heroin has historically been associated with lower socioeconomic groups, but the demographics have shifted over the last several decades. Heroin has become far more prevalent in non-urban communities, and the highest increases in heroin use have been in a surprising demographic: non-Hispanic white men. Furthermore, heroin abusers are getting younger, with users aged 18 to 44 having the highest rates of heroin-related deaths at 7.0 per 100,000 persons.[3] In 1 study of the regional and demographic differences in prescription-opioid and heroin-related overdose, heroin overdose rates were noted to be highest in the Midwest and Northeast regions. The study also suggested that new and younger heroin users may be more vulnerable to heroin-related overdoses because of the transition from prescription opioid use to heroin.[2]

The true incidence of OPIAD is difficult to ascertain because symptoms are often non-specific, if present at all. However, small studies have placed the prevalence of OPIAD at 90% in symptomatic men[4] and 53% in asymptomatic men on chronic opioid therapy.[5] These numbers suggest the need for a high index of suspicion in these patients, and providers should use laboratory tests to diagnosis the condition.

PATHOPHYSIOLOGY OF OPIOID-INDUCED HYPOGONADISM

Opioids exert their analgesic effect through binding and activation of μ-receptors in the presynaptic regions of the periaqueductal gray region, ventromedial hypothalamus, and superficial dorsal horn of the spinal cord. Activation of μ-receptors in other parts of the body produce several well-known side effects, which include dizziness, constipation, urinary retention, nausea, and respiratory depression.[6] Hypogonadism, perhaps the least well-known and investigated effect of chronic opioid use, has been increasingly reported in both men and women chronically taking opioids.

The hypothalamic–pituitary–gonadal axis plays a critical role in the development and regulation of the reproductive system. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile manner. The pituitary gland responds by releasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate Leydig cells and Sertoli cells, respectively. Fluctuations in the axis cause alterations in sex hormone release, which can have considerable local and system effects. Opioids act on this axis centrally by binding to μ-receptors in the hypothalamus, interrupting the pulsatile release of GnRH and causing downstream effects that limit the production of testosterone, resulting in hypogonadal effects such as decreased libido, erectile dysfunction, and loss of muscle mass.[7]

Opioids act on the hypothalamic–adrenal axis by decreasing dehydroepiandrosterone sulfate (DHEAS) production by the adrenals. Known inhibitors of corticotropin-releasing hormones (CRH), opioids have been reported to lower DHEAS levels in a dose-related pattern, suggesting that decreased CRH may also play in a role in OPIAD.[8] Dehydroepiandrosterone and DHEAS are endogenous precursors to more potent androgens such as testosterone and dihydrotestosterone. Their deficiency can also produce fatigue, depression, weakness, and sexual dysfunction, compounding the symptoms of OPIAD.

Opioids also directly affect the testes. Activation of μ-receptors present on human spermatozoa, predominantly in the plasma membrane of the sperm head and middle tail regions, lead to decreased sperm motility.[9] Studies have shown that opium consumption has significant deleterious effects on semen parameters and sperm chromatin, as measured by the DNA fragmentation index. It has also been demonstrated that chronic opioid users, in comparison to healthy age-matched volunteers, had significantly decreased sperm concentration (22 million vs 66 million/mL), increased DNA fragmentation (36% vs 27%), and significantly decreased levels of catalase-like and superoxide-dismutase activity.[10]

Alosi et al[11] demonstrated a change in the expression of testosterone catabolic enzymes in mice treated with morphine. The study showed that morphine may have long-lasting genomic effects on 5-alpha reductase and P-450 aromatase, increasing their expression in the liver, testes, and brain. In songbirds, testosterone levels and androgen receptor expression in the medial preoptic nucleus increase in the springtime and correlate positively with sexually motivated songs.[12] Cordeset et al[13] demonstrated that opioid release and μ-receptor expression in the same region inhibits sexually motivated songs. These animal models suggest that opioids affect sexual behavior and expression at multiple points, including at the mRNA level.

The literature reports an incidence of hypogonadism ranging between 50% and 90% in chronic opioid abusers.[14] The effect of the opioids on testosterone level has a quick onset and appears to be reversible.[15,16] Rubenstein et al[5] examined 81 men without previous diagnosis of hypogonadism on stable opioid doses for a minimum of 3 months. The incidence of hypogonadism was significantly associated with the duration of action of the opioids (74% vs 34%) but not the total daily dose. The authors proposed that long-acting opioids lead to stable serum opioid levels, which causes more cumulative GnRH suppression in comparison to shorter-acting opioids.

DIAGNOSIS

There is no definitive guideline for the diagnosis of OPIAD. However, as with other medical conditions, a good first step is obtaining a thorough history. Patients with hypogonadism may complain of increased fatigue, reduced sense of vitality, depressed mood, weight gain, and decreased muscle mass. However, these

symptoms are non-specific and may be attributed to other causes in patients with OPIAD, such as their underlying chronic pain condition or natural aging. Furthermore, patients may be hesitant to discuss more specific signs and symptoms of low testosterone such as erectile dysfunction, difficulty achieving an orgasm, reduced intensity of orgasm, and diminished ejaculatory volume. These difficulties with identifying men with OPIAD likely deflate the true prevalence of hypogonadism in men with chronic opioid use and underscore the need for a thorough history in these men, including history of opioid use.

Because of the non-specific nature of the symptoms associated with androgen deficiency in opioid users, serum testosterone levels should be obtained. The accepted lower limit of normal total testosterone is between 300 and 350 ng/dL.[17] A meta-analysis performed by Bawor et al[18] showed that about 50% of men taking opioids have testosterone suppression. The mean total testosterone in the opioid group was 165 ng/dL lower than that of the control group ($P < .0001$). Early-morning samples should be collected, and if abnormal results are found, repeat samples should be obtained. Other hormones such as sex hormone binding globulin, LH, FSH, and prolactin can help identify where along the hypothalamic–pituitary–gonadal axis the lesion lies and if there are other causes of hypogonadism.

Hypogonadism is traditionally subcategorized as primary, secondary, or tertiary. Primary hypogonadism is the result of testicular failure and is the most common cause of hypogonadism. Because of the loss of negative feedback on the central nervous system, the testes fail to produce an adequate amount of testosterone, which leads to systemic effects and an increase in gonadotropins (LH and FSH).[7] Secondary and tertiary hypogonadism result from central defects in the hypothalamus–pituitary axis at the level of the hypophysis and hypothalamus, respectively. Laboratory values often show a decrease in both testosterone as well as gonadotropins. Because the mechanism of action for OPIAD is rooted at the hypothalamic level with the loss of pulsatile GnRH release, OPIAD is classified as a cause of tertiary hypogonadism.

TREATMENT

The first-line treatment for OPIAD should include diet and lifestyle modifications. Decreasing opioid dosages or replacing opioids with NSAIDs or other non-narcotic painkillers are also critical components of the initial approach and can be very effective because of the dose-dependent relationship on the hypothalamic–pituitary–gonadal axis. If these conservative measures fail, replacement of the deficient hormones can be considered.[19] Because many patients require opioids to manage pain, tapering or eliminating opioid dose may be problematic. One option that has been pursued is the cycling of different opioids and avoidance of long-acting opioids. Rubinstein et al[5] identified a higher incidence of OPIAD in those taking long-acting (74%) rather than short-acting (34%) opioids. In patients who are persistently symptomatic and hypogonadal, androgen replacement therapy should be considered. Urologists should also be aware that, although not common, opioid dependence and overdose can result after urologic surgery. Shah et al[20] recently demonstrated that 0.09% of urologic patients experience opioid-related complications within 1 year of a procedure. Independent risk factors include younger age, history of depression, length of hospital stay, and major renal surgery.[20] Patients at higher risk for opioid dependence should be appropriately counseled and managed with non-opioid analgesics when possible.

Testosterone replacement therapy (TRT) is a mainstay in the treatment of symptomatic, hypogonadal men. Several retrospective and prospective studies have been conducted to assess the efficacy of TRT in men with OPIAD, although the optimal replacement therapy has not been studied in this population. Transdermal gels, patches, and injections have all been used with varying degrees of success. There have not been any studies between the different preparations or dosages of TRT. Basaria et al[21] conducted a double-blind, parallel-group, placebo-controlled trial randomizing hypogonadal men on opioids for chronic non-cancer pain to 5g transdermal testosterone gel or placebo. The study found that men treated with testosterone gel had an improvement in sensitivity to hyperalgesia, sexual desire, and improvement in body composition, although there was no in-group difference in self-reported pain. Other studies of TRT in men with OPIAD have reported statistically significant increases in testosterone levels as well as improvements in validated questionnaires such as the Brief Male Sexual Function Inventory and the Watts Sexual Function Questionnaire for Men.[22,23] Oral testosterone is susceptible to hepatic first-pass effect and is associated with hepatotoxicity. Sorting through the various available formulations currently available and endorsed by the Endocrine Society, the optimal testosterone replacement regimen should be chosen based on cost, patient preference, pharmacokinetics, and treatment burden.[24]

- **Intramuscular testosterone enanthate or cypionate, 75–100 mg every week or 150–200 mg every 2 weeks**
  - This formulation is the least expensive of the options but has the drawback of causing a steep rise in serum testosterone levels to supra-physiological levels followed by a gradual drop back to hypogonadal levels by the end of the dosing interval. The variations in testosterone levels are accompanied by swings in mood and libido that are sometimes difficult to tolerate. This is also the formulation most likely to cause polycythemia in the first few months of therapy.[25] The once-a-week dosing regimen is recommended for patients who experience particularly severe adverse events from fluctuating testosterone levels. Providers should be cognizant of the use of needles in patients recovering from heroin addiction. In patients for whom needles may serve as a trigger for relapse, other formulations should be considered.
- **Transdermal testosterone patches, 1 or 2 5-mg applied nightly**
  - The patches allow for a good approximation of normal circadian serum testosterone levels, but the site of

administration should be regularly examined for signs of irritation or allergic reaction.

- **1% testosterone gel 30−120 mg daily**
  - Patients should be aware that the gel is susceptible to secondary transfer via skin-to-skin contact and is flammable until dry. The gels are supplied as meter-dosed pumps that allow for relatively flexible titrations of dosing based on serum testosterone levels measured 2 weeks after initiation of treatment.
- **Subcutaneous testosterone pellets, varied dosing, interval injection of 3-6 months**[26]
  - Subcutaneous implantation of testosterone pellet improves compliance and eliminates the risk of secondary transfer. Patients should be informed that pellet extrusion and local site infection are rare but possible adverse events.

Clinicians who start their patients on TRT should obtain baseline testosterone, free testosterone, complete blood count, prostate-specific antigen, LH/FSH, and prolactin. Patients who desire fertility should be counseled that exogenous testosterone administration will lead to detrimental effects on their semen quality. Patients should have repeat labs drawn 3 to 6 months after initiation of therapy and then at 3- to 12-month intervals thereafter.[24] Frequent follow-up is essential to assess adequate response to therapy as well as to monitor for any metabolic or prostate-specific adverse events. Because the goal of therapy is to reduce symptoms, patients should also be given quality-of-life questionnaires to assess response to treatment beyond laboratory values.

The literature suggests that TRT is an effective treatment for men with OPIAD, but clinicians should be aware that there are associated adverse events such as polycythemia, sleep apnea, and reductions in high-density lipoprotein (HDL). Male-specific adverse events include azoospermia, gynecomastia, and priapism. Furthermore, patients with benign prostatic hyperplasia should be notified that obstructive symptoms may worsen, and acute urinary retention may develop with treatment. The use of TRT has not been shown to increase the risk of developing prostate cancer. However, testosterone treatment should not be used in patients with known prostate cancer and should be used extremely cautiously in those with suspected cancer.[27]

Questions have been raised regarding the increased risk of cardiovascular events in patients on TRT. Basaria et al[28] found that hypogonadal men aged 60 to 63 who underwent coronary angiography and subsequently started TRT were significantly more likely to suffer cardiovascular endpoints over 3 years. However, the study was limited by an inconsistent pattern of adverse events as well as a small number of overall events. A meta-review of 51 studies evaluating the adverse effects of testosterone in men found that the testosterone groups were associated with a significant increase in hematocrit and hemoglobin and decrease in HDL. However, there was no difference in mortality or major cardiovascular events.[29] Huang et al[30] looked at the effects on TRT on cardiometabolic parameters in men with OPIAD and found that metabolic parameters such as lipid profile, fasting glucose, and C-reactive protein were equal between groups whereas body composition improved in the testosterone group. Overall, the cardiovascular data related to TRT, particularly in the OPIAD population, is limited by short follow-up. A double-blinded, randomized, multicenter trial may be needed to assess the true risk.

Studies have demonstrated that opioids and estrogen activate common signaling pathways on the molecular level.[31] For example, the opioid receptor antagonist naloxone has been shown to inhibit breast cancer growth in mice by modulating estrogen receptors.[32] The crosstalk between the opioid and estrogen signaling pathways suggests that there may be a mechanism by which opioids suppress testosterone levels by inducing downstream effects of estrogen.

Clomiphene citrate (CC) is a selective estrogen receptor modulator that increases the level of endogenously produced testosterone by blocking the binding of estrogen at the level of hypothalamus. As a result, central production and release of GnRH is stimulated and there is a resultant increase in LH/FSH and downstream endogenous testosterone. CC has long been used by urologists for treatment of hypogonadism, particularly in men who wish to preserve their fertility. Studies have suggested that CC is effective at increasing testosterone levels with relatively few side effects.[33,34] Furthermore, Hussein et al[35] have discussed the benefits of CC use in men with non-obstructive azoospermia, demonstrating an increase in sperm counts and success rate of testis sperm retrieval. It should be noted, however, that CC has primarily been used to enhance fertility in women and has not been evaluated by the FDA for use in men with hypogonadism or infertility. Anastrozole is a reversible inhibitor of the aromatase enzyme that decreases the conversion of peripheral androgens to estrogens. Like CC, it has been used with some success in hypogonadal men with increased estradiol levels. Further molecular and clinical studies need to be conducted to elucidate the exact relationship between opioid use and estrogen levels and the role of CC and anastrozole in the OPIAD population.

CONCLUSION

The use and abuse of opioids is a critical global concern today. The chronic use of these medications can lead to hypogonadotropic hypogonadism, an underappreciated side effect. When evaluating patients for infertility or sexual dysfunction, it is important to get a complete medical history including medications, and to inquire about drug use, illicit or otherwise. Men on opioid treatment should be monitored for OPIAD while on therapy. Screening with validated questionnaires should be considered for all men receiving therapy. Diagnosis is made based on accepted laboratory values of testosterone deficiency. During the evaluation process, other causes of secondary hypogonadism including metabolic syndrome should be carefully assessed.

Although there is a lack of prospective randomized trials on treatment of OPIAD, current experience and knowledge base on the treatment of secondary hypogonadism can be used for guidance. A multidisciplinary care team is optimally utilized for management. Treatment options include opioid cessation with alternative pain control, use of short-acting narcotics and, when appropriate, testosterone replacement therapy. Exogenous testosterone is available in multiple formulations with generally similar efficacy in this patient population. The advantages and disadvantages of each formulation should be discussed with the patient and the appropriate treatment chosen based on shared decision-making and comprehensive counseling. CC and anastrozole have been used off-label to increase endogenous testosterone in hypogonadal men hoping to preserve fertility, although there is no data yet on their use in the OPIAD population. Literature on cardiovascular risks of testosterone replacement is conflicting and thus a detailed discussion before initiation of therapy is mandatory. With increased awareness of OPIAD, larger prospective, randomized studies are needed to help guide physicians for the diagnosis and management of this disease process.

Corresponding Author: Hossein Sadeghi-Nejad, MD, Surgery, Division of Urology, New Jersey Medical School, 185 South Orange Avenue MSBG536, Newark, NJ 07103. Tel: 973-972-4488; Fax: 973-395-7197; E-mail: hossein@ix.netcom.com

Conflict of Interest: The authors report no conflicts of interest.

Funding: None.

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design
Alan Hsieh; Lorenzo DiGiorgio; Mary Fakunle; Hossein Sadeghi-Nejad

(b) Acquisition of Data
Alan Hsieh; Lorenzo DiGiorgio; Mary Fakunle; Hossein Sadeghi-Nejad

(c) Analysis and Interpretation of Data
Alan Hsieh; Lorenzo DiGiorgio; Mary Fakunle; Hossein Sadeghi-Nejad

Category 2

(a) Drafting the Article
Alan Hsieh; Lorenzo DiGiorgio; Mary Fakunle; Hossein Sadeghi-Nejad

(b) Revising It for Intellectual Content
Alan Hsieh; Lorenzo DiGiorgio; Mary Fakunle; Hossein Sadeghi-Nejad

Category 3

(a) Final Approval of the Completed Article
Alan Hsieh; Lorenzo DiGiorgio; Mary Fakunle; Hossein Sadeghi-Nejad

REFERENCES

1. Kolodny A, Courtwright DT, Hwang CS, et al. The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction. **Annu Rev Public Health 2015;36:559-574.**
2. Unick GJ, Ciccarone D. US regional and demographic differences in prescription opioid and heroin-related overdose hospitalizations. **Int J Drug Po 2017;46:112-119.**
3. Lucyk SN, Nelson LS. Toxicosurveillance in the US opioid epidemic. **J Drug Po 2017:5-57.**
4. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. **Cancer 2004;100:851-858.**
5. Rubinstein AL, Carpenter DM, Minkoff JR. Hypogonadism in men with chronic pain linked to the use of long-acting rather than short-acting opioids. **Clin J Pain 2013;29:840-845.**
6. Ali K, Raphael J, Khan S, et al. The effects of opioids on the endocrine system an overview. **Postgrad Med J 2016;92:677-681.**
7. Khera M, Broderick GA, Carson CC III, et al. Adult-onset hypogonadism. **Mayo Clin Proc 2016;91:908-926.**
8. Zhang GF, Ren Y, Sheng L, et al. Dysfunction of the hypothalamic—pituitary—adrenal axis in opioid dependent subjects: Effects of acute and protracted abstinence. **Am J Drug Alcohol Abuse 2008;34:760-768.**
9. Ragni G, De Lauretis L, Bestetti O, et al. Gonadal function in male heroin and methadone addicts. **Int J Androl 1988;11:93-100.**
10. Safarinejad MR, Asgari SA, Farshi A, et al. The effects of opiate consumption on serum reproductive hormone levels, sperm parameters, seminal plasma antioxidant capacity and sperm DNA integrity. **Reprod Toxicol 2013;36:18-23.**
11. Aloisi AM, Ceccarelli I, Fiorenzani P, et al. Aromatase and 5-alpha reductase gene expression: Modulation by pain and morphine treatment in male rats. **Mol Pain 2010;26:69.**
12. Cordes MA, Stevenson SA, Driessen TM, et al. Sexually-motivated song is predicted by androgen- and opioid-related gene expression in the medial preoptic nucleus of male European starlings (Stumus vulagaris). **Behav Brain Res 2015;278:12-20.**
13. Ventura-Aquino E, Paredes RG. Animal models in sexual medicine: The need and importance of studying sexual motivation. **Sex Med Rev 2017;5:5-19.**
14. Schneider J. Hypogonadism in men treated with chronic opioids. **Arch Phys Med Rehabil 2008;89:1414.**
15. Woody G, McLeilan T, O'Brien C, et al. Hormone secretion in methadone dependent and abstinent patients. **NIDA Res Monogr 1988;81:216-223.**
16. Mendelson JH, Meyer RE, Ellingboe J, et al. Effects of heroin and methadone on plasma cortisol and testosterone. **J Pharmacol Exp Ther 1975;195:296-302.**

17. Montorsi F, Adaikan G, Becher E, et al. Summary of the recommendations on sexual dysfunctions in men. **J Sex Med 2010;7:3572-3588.**
18. Bawor M, Bami H, Dennis BB, et al. Testosterone suppression in opioid users: a systematic review and meta-analysis. **Drug Alcohol Depen 2015;149:1-9.**
19. Daniell HW. Hypgonadism in men consuming sustained-action oral opioids. **J Pain 2002;3:377-384.**
20. Shah AS, Blackwell RH, Kuo PC, et al. Rates and risk factors for opioid dependence and overdose after urological surgery. **J Urol 2017;198:1130-1136.**
21. Basaria S, Travison TG, Alford D, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. **Pain 2015;156:280-288.**
22. Blick G, Khera M, Bhattacharya RK, et al. Testosterone replacement therapy outcomes among opioid users: the Testim Registry in the United States (TRiUS). **Pain Med 2012; 13:688-698.**
23. Daniell HW, Lentz R, Mazer NA. Open-label pilot study of testosterone patch therapy in men with opioid-induced androgen deficiency. **J Pain 2006;7:200-210.**
24. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. **J Clin Endocrinol 2010;95:2536-2559.**
25. Dobs AS, Meikle AW, Arver S, et al. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. **J Clin Endocrinol Metab 1999;84:3469-3478.**
26. Kaminetsky JC, Moclair B, Hemani M, et al. A phase IV prospective evaluation of the safety and efficacy of extended release testosterone pellets for the treatment of male hypogonadism. **J Sex Med 2011;8:1186-1196.**
27. Smith HS, Elliot JA. Opioid-induced androgen deficiency (OPIAD). **Pain Physician 2012.**
28. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. **N Engl J Med 2010;363:109-122.**
29. Fernandez-Balsells MM, Murad MH, Lane M, et al. Adverse effects of testosterone therapy in adult men: A systematic review and meta-analysis. **J Clin Endocrinol Metab 2010; 95:2560-2575.**
30. Huang G, Travison T, Maggio M, et al. Effects of testosterone replacement on metabolic and inflammatory markers in men with opioid-induced androgen deficiency. **J Clin Endocrinol 2016;85:232-238.**
31. Lee CW, Ho I. Sex differences in opioid analgesia and addiction: Interactions among opioid receptors and estrogen receptors. **Mol Pain 2013;9:45.**
32. Farooqui M, Geng ZH, Stephenson EJ, et al. Naloxone acts as an antagonist of estrogen receptor activity in MCF-7 cells. **Mol Cancer Ther 2006;5:611-620.**
33. Katz DJ, Nabulsi O, Tal R, et al. Outcomes of clomiphene citrate treatment in young hypogonadal men. **BJU Int 2012; 110:573-578.**
34. Shabsigh A, Kang Y, Shabsign R, et al. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. **J Sex Med 2005;2:716-721.**
35. Hussein A, Ozgok Y, Ross L, et al. Clomiphene administration for cases of nonobstructive azoospermia: a multicenter study. **J Androl 2005;26:787-791.**