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MEN'S HEALTH (A DABAJA, SECTION EDITOR)

Opioid-Induced Androgen Deficiency (OPIAD): Diagnosis, Management, and Literature Review

Timothy K. O'Rourke Jr[1] · **Matthew S. Wosnitzer**[2]

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Abstract Opioid-induced androgen deficiency (OPIAD) was initially recognized as a possible consequence of opioid use roughly four decades ago. Long-acting opioid use carries risks of addiction, tolerance, and systemic side effects including hypogonadotropic hypogonadism with consequent testosterone depletion leading to multiple central and peripheral effects. Hypogonadism is induced through direct inhibitory action of opioids on receptors within the hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-adrenal (HPA) axes as well as testosterone production within the testes. Few studies have systematically investigated hormonal changes induced by long-term opioid administration or the effects of testosterone replacement therapy (TRT) in patients with OPIAD. Clomiphene citrate, a selective estrogen receptor modulator (SERM), is a testosterone enhancement treatment which upregulates endogenous hypothalamic function. This review will focus on the pathophysiology, diagnosis, and management of OPIAD, including summary of literature evaluating OPIAD treatment with TRT, and areas of future investigation.

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✉ Matthew S. Wosnitzer
matthew.wosnitzer@ynhh.org

Timothy K. O'Rourke, Jr
tkorourke@quinnipiac.edu

[1] Frank H. Netter MD School of Medicine, Quinnipiac University, 370 Bassett Road, North Haven, CT 06473, USA

[2] Northeast Medical Group Urology / Male Reproductive Medicine and Surgery, Yale New Haven Health, 425 Post Road, Fairfield, CT 06824, USA

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Introduction

Opioids are among the most frequently prescribed analgesic drugs which may lead to multiple side effects including hypogonadotropic hypogonadism with central (decreased attention, decreased libido, fatigue, depressive state) and peripheral effects (muscle hypotrophy, osteoporosis, anemia, erectile dysfunction, delayed ejaculation) [1, 2]. Opioid use and abuse has been a societal issue since 3400 B.C. with Sumerians of Mesopotamia with spread to all major civilizations through present times [3]. The use of long-acting opioids, including morphine sulfate, oxycodone, fentanyl, and methadone, although effective for pain control, carries risks of addiction, tolerance, and systemic side effects including nausea, itching, constipation, and hypogonadotropic hypogonadism with consequent testosterone depletion leading to multiple central and peripheral effects affecting men and to some lesser extent women (although men will be the focus of this review). Although opioid-induced androgen deficiency (OPIAD) occurs with high frequency and persistence, the condition frequently remains undiagnosed in the pain clinic [4, 5].

As the opioid prescription rate continues to increase for chronic non-malignant and malignant pain syndromes, the rates of associated adverse effects including opioid-induced androgen deficiency (OPIAD) continue to increase. OPIAD, detailed decades ago, was further described in 1973, when it was observed that males abusing opioids had lower sexual function, libido, and lower levels of serum sex hormones than peers not abusing such illicit substances [6, 7]. There are no official clinical guidelines for diagnosis or treatment of

opioid-induced androgen deficiency from the American Urological Association or other professional societies. Hypogonadotropic hypogonadism (incidence cited between 21 and 86 % among patients with chronic opioid use) typically occurs within several hours to weeks of treatment initiation (doses >100–200 mg of oral morphine equivalents per day) with eventual castrate testosterone levels [8] seen in a dose-dependent manner [1, 9, 10]. Once opioid treatment is ceased, testosterone may recover within 24 to 72 h, but hypogonadism may persist for months or even years depending on chronicity of opioid use [11–13].

The causes, pathophysiology, and implications of OPIAD are striking and pertinent in the current milieu of widespread and increasing rates of opioid prescription and abuse [14, 15].

Hypogonadotropic hypogonadism in the setting of concomitant OPIAD and chronic pain may be considered multifactorial in etiology. In addition to opioid effects on the HPG axis, the experience of chronic pain itself has also been associated with androgen deficiency, confounding the association of low testosterone with opioid pain medication use and raising the question of whether androgen deficiency is also associated with pain sensitivity and perception [16, 17]. Further, opioids can themselves induce a state of hyperalgesia, characterized by increased sensitivity to pain rather than pain relief—an effect not thoroughly understood to date. In those who are androgen deficient, replacement therapy may lead to an improvement in this state of increased nociception [18]. It has also been postulated that certain opioid medications are more likely to induce androgen deficiency than others, although some authors have questioned this theory [19–22].

Several clinical studies have evaluated treatment strategies for those diagnosed with OPIAD, discussed in this review, although additional prospective trials are needed to determine the most effective management protocol. OPIAD serves as a further impetus driving health systems and the federal government to advocate reform in the prescribing practices of opioids for chronic pain [23]. This is vitally important especially considering the dramatic increase of opioid prescribing and abuse that has been observed in recent years [24]. Patients require education from physicians regarding the impact that opioids may have on the endocrine system with particular emphasis on androgen deficiency and associated symptoms. The current understanding and recommendations with regard to the incidence, pathophysiology, diagnosis, and treatment of OPIAD will be detailed in this review.

Methods

A PubMed (PMID) search was undertaken using the following MeSH terms and included all English language publications between dates of 1/1960 and 5/2016: “analgesics, opioid AND testosterone,” “analgesics, opioid AND hypogonadism,” “pain AND testosterone,” “pain AND hypogonadism,” “analgesics, narcotic AND testosterone,” and “analgesics, narcotic AND hypogonadism.” PMID searches of “opioid induced androgen deficiency” and “opioid associated androgen deficiency” were also undertaken specifically within the aforementioned time period. Finally, an unrestricted PMID search of the phrase “opioids AND hypogonadism AND testosterone” without exclusion criteria or time limitation was performed to increase the yield of prospective trials previously published for the treatment of OPIAD with exogenous testosterone. Studies deemed pertinent to opioid-induced androgen deficiency were included in this review, with particular emphasis placed on prospective trials evaluating the effectiveness of TRT in treating this condition.

Incidence

The prevalence of OPIAD had been described as high as 90 % among those receiving chronic opioid therapy in one study, in which 40 patients with a history of cancer were studied: 20 patients received chronic opioids and the others received no opioids. Ninety percent (18/20) of those taking opioids experienced symptoms of hypogonadism with laboratory evaluation of median luteinizing hormone (LH) and testosterone significantly lower than those not taking these medications (95 % CI 65–98 %). Forty percent (8/10) of those not taking opioids were found to be hypogonadal (95 % CI 19–64 %) [10]. The incidence of OPIAD is expected to be higher than any reported figure as the clinical signs and symptoms may go unrecognized in the absence of routine laboratory testing [15]. A more recent study elucidated the prevalence of hypogonadism in a population of 81 males with chronic pain on opioids to be 53 % (defined as total T <250 ng/dl) [21]. A 2011 study reported the estimated United States prevalence of OPIAD to be >5 million men with non-malignant pain [25].

Pathophysiology

Central Inhibitory Effects of Opioids

The pathophysiology of OPIAD has been well established to date and has been shown to be multifactorial. Morphine and morphine-like peptides produce their analgesic effect mainly through mu (μ) receptors, which exist predominantly presynaptically in the periaqueductal gray region, medial preoptic area, ventromedial hypothalamus, and superficial dorsal horn of the spinal cord. Opioids bind to mu receptors in the hypothalamus, inhibiting the production and release of GnRH, thus decreasing LH and follicle-stimulating hormone (FSH) secretion from the anterior pituitary. Subsequently, testosterone is decreased with consequences described above [9, 26–29]. Pulse frequency can be returned to normal by co-administration of opioid antagonists in adult men, and opioid antagonists increased LH pulse frequency when given

independently [30, 31]. FSH may be less affected or not affected compared to LH [32]. The effect may be different using different routes, types, and dosages of opioid medications with more pronounced effects from intrathecal opioids than oral agents.

Studies indicate that central opioid mu receptor stimulation prevents penile erection by inhibiting mechanisms via central oxytocinergic neurotransmission [33]. In rats, morphine injected into the paraventricular nucleus inhibits non-contact penile erections and impairs copulation. These consequences of morphine are mediated by prevention of increased nitric oxide production occurring in the paraventricular nucleus during sexual activity [34]. Morphine also prevents apomorphine-, oxytocin-, NMDA- and non-contact-induced penile erection by inhibiting NOS activity in the paraventricular nucleus [35].

Additional Endocrine System Inhibition by Opioids

In addition to affecting the hypothalamic-pituitary gonadal (HPG) axis, opioids interfere with the hypothalamic-pituitary adrenocortical (HPA) axis through decreasing the responsiveness of the anterior pituitary to CRH and inhibition of DHEAS production through direct activity in the adrenal gland [36–38]. Acute and chronic opioid use also is known to increase serum prolactin [39], decreased GH [9], increased TSH [40], and inhibit ACTH secretion [41] in humans, but has not been found to affect thyroid function tests. HDL has also been shown to be significantly decreased with chronic opioid use [9]. These fundamental principles had been elucidated over the course of the last few decades [7, 42].

Peripheral Inhibitory Effects of Opioids

Opioids inhibit spermatogenesis and testosterone production through direct activity in the testes [28, 29, 31, 43–46]. Mu opioid receptors have been identified in human spermatozoa, predominantly in the plasma membrane of the sperm head and middle tail regions [47]. Additionally, opioid peptides (endorphins and enkephalins) are found in semen and in sperm, while enzymes for degradation of opioids are present in human semen [48, 49]. Endogenous opioids (met-enkephalin, B-endorphin) and exogenous opioids (morphine) are recognized to diminish sperm motility in vitro via opioid receptors [50, 51]. Chronic heroin users have been identified to have decreased sperm motility on semen analysis [52]. An evaluation of 140 males with chronic opioid use revealed significantly decreased sperm concentration (22 vs. 66 million/ml), increased DNA fragmentation (36 vs. 27 %), and significantly decreased levels of catalase-like and superoxide-dismutase activity when compared with healthy age-matched volunteers [53]. The direct effect of opioid peptides on sperm and fertility still requires additional investigation.

Effect of Opioids on Bone Mineral Density

Although hypogonadism itself may result in decreased bone mineral density (BMD), other mechanisms related to opioids themselves have been investigated [54]. In one study, not only were all three opioid receptors identified in murine osteoblasts, but introduction of morphine caused a decreased production of osteocalcin, a protein associated with osteoblastic activity [55]. Interestingly, recent work demonstrated the role osteocalcin plays in the production of testosterone as well as the so-called bone-testis axis [56]. Osteocalcin appeared to be positively correlated with total testosterone. In the same study, testosterone was associated with blood alkaline phosphatase and C-terminal telopeptides of type 1 collagen, markers of bone activity [57].

A recent cross-sectional study by Gotthardt et al. in Switzerland identified decreased BMD in patients with chronic (>10 years) opioid dependency ($n = 144$) compared to a control group ($n = 35$) (0.929 ± 0.129 vs. 1.220 ± 0.134, $p < 0.01$). Further, the rates of osteoporosis, osteopenia, and low bone mass were increased in the study arm vs. control (31 ± 29.2 vs. 0 % ($p = 0.006$), 51 ± 48.1 vs. 8 ± 34.8 % ($p = 0.021$), and 25 ± 65.8 vs. 5 ± 41.7 % ($p < 0.001$), respectively). Free testosterone was also identified to play an independent role bone mass in this study population on multivariate analysis (β estimate 0.000241, $p = 0.0201$), thus highlighting its importance as a determinant in bone health [58]. These data are concerning and as previously discussed and are likely due to associated hypogonadism and direct inhibitory effects on the bone observed in those taking chronic opioids. The importance of TRT in patients with osteoporosis and hypogonadism is well established, with improvements observed in outcomes such as fertility and bone mineral density, among others [59•].

Results

A total of 428 unique publications were acquired through the methods previously described, of which only one prospective randomized double-blinded placebo-controlled trial was identified, yielding two published studies [60••, 61••]. Two other prospective trials were published in 2006 and 2011 and were included in this review [42, 62]. Two additional studies evaluating the effects of exogenous testosterone supplementation in the treatment of OPIAD, published in 2012 and 2015, were also identified [59•, 63•]. Table 1 outlines the study design and results of the primary studies identified.

The testosterone and pain (TAP) trial conducted by Basaria et al. was a double-blinded placebo controlled prospective trial that sought to elucidate the effectiveness of testosterone in the formulation of 5 g 1 % gel in those with OPIAD, as defined by morning serum testosterone <350 ng/dl (higher testosterone threshold than some society recommendations described

Table 1 Summary of the primary articles evaluating testosterone replacement therapy in patients with OPIAD

	Study design	Subjects	Baseline testosterone (mean ± SD unless otherwise noted)	Etiology/type of opioid(s) used	Testosterone preparation	Outcome of T rise (treatment group) (mean ± SD)
Huang et al. 2016 [61]	"Single-centre, parallel group, placebo-controlled, double-blind randomized trial"	64 enrolled and completed Non-malignant pain	Testosterone arm: Total T: 7.7 ± 3.0 nmol/l Free T: 153 ± 78 pmol/l Placebo arm: Total T: 8.2 ± 3.4 nmol/l Free T: 149 ± 67 pmol/l	20 mg hydrocodone (or morphine equivalent): ≥4 weeks	5–7.5 g AndroGel® 1 % transdermal testosterone gel	Total T: 27 ± 19 nmol/l (p value not calculated) Free T: 656 ± 525 pmol/l (p value not calculated)
Basaria et al. 2015 [60]	"Randomized, double-blind, placebo-controlled, single-center parallel group trial"	84 enrolled, 65 completed Non-malignant pain	Testosterone arm (median): Total T: 243 ng/dl Free T: 47 pg/ml Placebo arm (median): Total T: 251 ng/dl Free T: 43 pg/ml	20 mg hydrocodone (or morphine equivalent): ≥4 weeks	5–7.5 g AndroGel® 1 % transdermal testosterone gel	Total T: 790 ± 544 ng/dl ($p < 0.01$ vs. placebo)
Finch et al. 2015 [59]	Cross-sectional study	27 enrolled Non-malignant pain	Testosterone treatment: Serum T: 20.8 ± 4.5 nmol/l ($p < 0.001$ vs. no T treatment) Free T: 576 ± 149 pmol/l ($p < 0.005$ vs. no T treatment) No testosterone treatment: Serum T: 6.5 ± 1.1 nmol/l Free T: 114 ± 32 pmol/l	Intrathecal opioids, one of two regimens: (a) Morphine (range = 1–20 mg/day, mean 7.2 mg/day) (b) Hydromorphone (range = 1–20 mg/day, mean 4.15 mg/day)	Depot testosterone undecanoate 1000 mg/3 months ($n = 9$) Depot testosterone enanthate 250 mg (3×/week) ($n = 1$) Transdermal testosterone gel 50 mg/day ($n = 1$)	–
Blick et al. 2012 [63]	"Prospective, 12-month observational cohort registry"	90 reviewed Unspecified pain etiology	Total T: 280 ± 170 ng/dl Free T: 27 ± 39 pg/ml	Multiple regimens (note: 75/90 pts were on opioids ≥30 days): (a) Hydrocodone ($n = 41$) (b) Oxycodone ($n = 25$) (c) Morphine ($n = 6$) (d) Buprenorphine ($n = 4$) (e) Codeine ($n = 4$) (f) Propoxyphene ($n = 4$) (g) Oxymorphone ($n = 2$) (h) Tramadol ($n = 2$) (i) Fentanyl ($n = 1$) (j) Methadone ($n = 1$)	Testim® 1 % testosterone gel 5–10 g/day 5 g/day: $n = 57$–59 10 g/day: $n = 3133$	1 month Total T: >600 ng/dl ($p \leq 0.001$ vs. baseline) Free T: >150 pg/ml ($p \leq 0.001$ vs. baseline) 6 and 12 months: T rise not statistically significant vs. baseline due to lack of available data at 12-month follow-up ($n =$ 12 at 6 months and $n = 8$ at 12 months)
	Prospective single-arm trial		Total T: 1.16 ± 0.28 ng/ml	Epidural morphine ≥6 months		12 months

Table 1 (continued)

	Study design	Subjects	Baseline testosterone (mean ± SD unless otherwise noted)	Etiology/type of opioid(s) used	Testosterone preparation	Outcome of T rise (treatment group) (mean ± SD)
Aloisi et al. 2011 [62]		17 enrolled and completed Non-malignant pain	Free T: 4.33 ± 0.89 pg/ml Bioavailable T: 0.34 ± 0.1 ng/dl		5 g transdermal testosterone gel	Total T: 2.99 ± 0.47 ng/ml ($p < 0.01$ vs. baseline) Free T: 10.57 ± 1.88 pg/ml ($p < 0.05$ vs. baseline) Bioavailable T: .17 ± 0.34 ng/dl ($p < 0.05$ vs. baseline)
Daniell et al. 2006 [36]	Prospective single-arm trial	23 enrolled, 16 completed Non-malignant pain	Free Testosterone: 28.5 ± 18.6 pg/ml	≥6 months chronic opioids including one of four regimens (≥4 previous weeks): (a) ≥20 mg/day methadone (b) ≥30 mg/day oxycodone (c) ≥30 mg/day morphine (d) ≥25 μg/h fentanyl	Androderm™ testosterone transdermal patch First 12 weeks: 5 mg/day Second 12 weeks: 7.5 mg/day	72.8 ± 29.6 pg/ml ($p < 0.001$ vs. baseline) 120.2 ± 69.5 pg/ml ($p < 0.001$ vs. baseline, $p < 0.01$ vs. 5 mg/day)

herein). Of those completing the trial, 36 patients received TRT while 29 did not. At 14 weeks, the treatment group experienced statistically significant increases in serum total and free testosterone ($p < 0.01$) and sexual function ($p = 0.05$) with decreased fat mass ($p = 0.01$). The treatment group also experienced significantly improved tolerance to pain, specifically with thumb pressure stimulus ($p = 0.03$) and graded mechanical pinprick stimulus ($p = 0.05$). Initial tolerance to trapezius pressure stimulus and hand cold stimulus, as well as pain intensity 30 s after cold stimulus exposure, was also improved in the treatment group although the results were not significant ($p = 0.07$, 0.41, and 0.08, respectively). Brief pain inventory (BPI) scores, total and specifically regarding pain interference, were lower in the treatment arm although again the results were not significant ($p = 0.38$ and 0.21, respectfully) [60••].

Huang et al. studied 64 patients from the TAP trial with regard to metabolic and inflammatory markers in the setting of testosterone supplementation. This study examined the safety profile of TRT in the setting of OPIAD. The authors found no significant difference in total cholesterol, LDL cholesterol, triglycerides, HbA1c, fasting glucose, fasting insulin, adiponectin, leptin, and C-reactive protein (CRP) between those receiving testosterone ($n = 36$) and those who were not ($n = 28$) after 3 months. The authors did note that cardiovascular risk was not assessed in their study, however, and advocated for future studies to better elucidate this endpoint [61••].

Finch et al. examined the effect of hypogonadism on bone mineral density in the setting of chronic intrathecal opioids in 2015. Twenty-seven males with chronic pain, 11 being treated for hypogonadism with testosterone supplementation and 16 not being treated, were evaluated by dual-emission X-ray absorptiometry (DEXA) and had their serum baseline total, free testosterone, and sex hormone-binding globulin (SHBG) measured. Both T and Z scores for those receiving testosterone were higher than those not receiving such supplementation ($p = 0.006$ and 0.02, respectfully). Serum T and free T were higher, and SHBG was lower in those receiving testosterone ($p = 0.001$, 0.005, and 0.019, respectively) [59•].

Pain vs. Opioid Medication

There is evidence that the experience of pain itself may be associated with hypogonadism, independent of opioid use. Endogenous opiates play a major role in regulation of gonadotropins, through a tonic inhibitory control [26]. Endogenous opioids such as B-endorphin modulate GnRH pulse amplitude and frequency by presynaptic inhibition of GnRH terminals in the median eminence and interaction with adrenergic neurotransmission, respectively. It is not well established if increased sensitivity to pain is caused by low testosterone or alternatively is due to pain mediators inhibiting the production of androgens. In one study, blood plasma factors were evaluated between patients with chronic prostatitis/chronic pelvic

pain syndrome (CP/CPPS) ($n = 32$) and patients without CP/CPPS ($n = 37$). Baseline testosterone was found to be lower in those with CP/CPPS (6.18 ± 2.28 vs. 6.93 ± 1.66 ng/ml, $p = 0.014$). When controlling for patients with underlying comorbidities, the effect was again observed ($p = 0.047$) [16].

It may also be postulated that increased sensitivity to pain, related to low testosterone, leads to increased pain medication requirements, further propagating androgen deficiency. A consistent dose-response effect does not appear to be fully elucidated to date, however [11]. Rubinstein et al. confirmed that the risk of androgen deficiency is higher in those taking long-acting (57.0 %, 351/616) vs. short-acting (35.1 %, 340/969) opioids ($p < 0.001$, OR 3.39, 95 % CI 2.39–4.77) and with a dose increase, but this latter effect was observed more so in short-acting (OR 1.16, 95 % CI 1.09–1.23) than long-acting (OR 1.01, 95 % CI 1.01–1.02) opioids [22].

Diagnosis

There are no strict evidence-based guidelines regarding the diagnosis of OPIAD, with many of the sequelae of this condition unrecognized or attributed to chronic pain [15]. Testosterone deficiency diagnosis must be based on symptoms and serum testosterone levels measured by initial and repeat morning total testosterone level by a reliable assay with free testosterone and SHBG as indicated by clinical circumstances [64]. According to the International Congress of Sexual Medicine (ICSM) and Endocrine Society guidelines, generally accepted lower limit of normal total testosterone is 300 [64] to 350 ng/dl [65], while those with total testosterone <230 ng/dl usually benefit from testosterone treatment [65].

Bawor et al. performed a meta-analysis of the data surrounding decreased testosterone in those taking opioids and promoted the measurement of baseline testosterone when commencing opioid therapy in addition to testosterone monitoring throughout the treatment course. In their meta-analysis, the authors identified significantly lower total testosterone in males on opioids ($n = 607$) when compared to those not on opioids ($n = 1417$) (mean difference = −164.89, 95 % CI −245.47–84.08, $p < 0.0001$) [20]. In the event that testosterone suppression is evident through laboratory analysis, it may then be appropriate to commence treatment given the negative sequelae of androgen deficiency [1, 11]. Table 1 outlines the baseline testosterone of patients included in studies evaluating the effect of supplemental testosterone in treating OPIAD. Healy et al. recommended morning serum measurement of total testosterone with repeated measurement if abnormal and follow-up testing with free testosterone, SHBG, LH, FSH, and prolactin to increase diagnostic precision. The authors reported the normal total testosterone range as 300–800 ng/dl, similar to the accepted workup for low testosterone of any cause [66]. Given the high prevalence of opioid use, it would be unreasonable to assess androgen deficiency through measurement of testosterone in all patients. Thus, an alternative approach could be to screen all patients taking opioids for androgen deficiency with the validated 10-question androgen deficiency in aging males (ADAM) questionnaire with follow-up laboratory assessment (morning testosterone) if positive [67]. If low morning testosterone is identified and confirmed, additional hormones may be evaluated (depending on clinical scenario) including LH, FSH, estradiol, and prolactin.

Treatment

As displayed in Table 1, testosterone replacement therapy (TRT) has been assessed in OPIAD with varying preparations in small retrospective studies and few prospective studies (fewer than 280 patients) with beneficial effects on serum testosterone and QoL [9, 42, 6263•]. The majority of patients evaluated in these studies were suffering from chronic non-malignant pain; this was explicitly stated in all but the Blick et al. study. TRT has been shown to improve several parameters related to hypogonadism seen in OPIAD. Table 2 outlines the quality of life and symptom improvements studied in testosterone replacement therapy (TRT) trials previously described and demonstrates potential benefit to depression, erectile/sexual dysfunction, and pain perception. However, there is need for more consistent usage of validated questionnaires to assess multiple quality of life outcomes in both non-malignant and malignant pain syndromes.

While first-line treatment for low testosterone includes diet and exercise [68] and decreasing opioid dosage, in many cases, opioid medication cannot be stopped completely. In patients with symptomatic hypogonadism with persistently low testosterone that meets guideline criteria, testosterone replacement should be considered; however, the optimal testosterone preparation for OPIAD treatment has yet to be determined. Transdermal gels and patches as well as injection therapy have been studied and found to be effective as described in Table 1 similar to studies of hypogonadal men without pain and chronic narcotic use [63•, 64]. There have been no comprehensive comparisons between different preparations of TRT in OPIAD, and the dosage is determined based on standard accepted guidelines according to serum parameters and patient symptoms. The safety of testosterone supplementation in the setting of OPIAD was reviewed in one recent study [61••] and is likely similar to TRT safety in other populations with required full discussion of risk/benefit profile and contraindications [69–74]. The benefits of TRT in OPIAD may outweigh potential risks in many circumstances given the significant morbidity and quality of life (QoL) issues potentially facing those with hypogonadism, chronic pain, and chronic opioid use. Alternative pain regimens, such as non-steroidal anti-inflammatory drugs (NSAIDs), should especially be considered in patients in whom risks outweigh benefits of testosterone treatment [75]. There also appears to be promise related to decreased pain requirements in those receiving TRT as

Table 2 Validated instruments and selected outcomes of TRT measured in patients with OPIAD

	Validated instruments implemented	Selected outcomes	Rx difference (TRT vs. CTR or baseline)	*p* value
Basaria et al. 2015 [60]	Brief pain inventory (BPI)	Total score	−0.59	0.38
	International index of erectile function	"Pain interference score"	−0.59	0.21
		Sexual desire	1.07	0.05
		Erectile function	0.36	0.84
	Medical outcomes short study form-36	"Role limitations due to emotional problems"	20	0.08
		Social functioning	5.07	0.28
		"Role limitations due to physical health"	9.35	0.27
Blick et al. 2012 [63]	Brief male sexual function inventory (BMSFI)	Sexual function (1 month)	3.8 ± 1.8	0.04
		Sexual function (6 months)	7.6 ± 2.0	<0.001
		Sexual function (12 months)	6.7 ± 2.2	0.003
	Patient health questionnaire (PHQ-9)	Depression index (1 month)	~−2 ± 1	0.02
		Depression index (6 months)	~−3 ± 2	0.002
		Depression index (12 months)	~−6 ± 2	<0.001
Aloisi et al. 2011 [62]	Visual analogue scale (VAS)	Pain (12 months)	~−2.86	Not reported (not statistically significant)
	Italian pain questionnaire (QUID)	Total pain (12 months)	~−20.58	<0.01
	Margolis method (% body surface area pain)	Pain (12 months)	~0.22	Not reported (not statistically significant)
	Aging Males' Symptoms scale (AMS) questionnaire	"Sexual" component" (12 months)	~−3.72 (improved)	<0.03
	Profile of mood state (POMS)	"Depression-Dejection" component (12 months)	~1.58	Not reported (not statistically significant)
	Center for Epidemiological Studies Depression Scale (CES-D)	Depression index (12 months)	~1.57	Not reported (not statistically significant)
	Short form health survey (SF-36)	"Mental Index" (12 months)	~9	<0.04
Daniell et al. 2006 [36]	Androgen deficiency symptoms questionnaire (ADSQ)	Decreased libido (weighted, 24 weeks)	~−4.9 (improved)	<0.001
		Erectile dysfunction (weighted, 24 weeks)	~−4.8 (improved)	<0.01
	Watts sexual function questionnaire for men (Watts SFQ)	Total score (24 weeks)	~11.4 (improved)	<0.001
	Psychological general well-being index (PGWB)	Total score (24 weeks)	~16.6 < 0.01	
	Beck depression inventory, second edition (BDI-II)	Total score (24 weeks)	−7 (improved)	<0.01
	Brief pain inventory-short form (BPI-SF)	"Severity Score" (24 weeks)	~−	<1
		"Interference Score" (24 weeks)	~−1	<0.05

increased tolerance to pain was observed in the TAP trial in the treatment arm—this effect should be investigated in future randomized trials [60••]. The management plan for patients with complex clinical scenarios should be formulated by a multidisciplinary team including urology and pain management physicians.

Follow-up monitoring for patients being treated with TRT includes baseline assessment of total T and free T, complete blood count (CBC), prostate-specific antigen (PSA), estradiol, LH, FSH, and prolactin, with regular interval serum measurements of total testosterone, CBC, PSA, and estradiol, initially between 3 and 6 months after commencing treatment and every 3–12 months thereafter, in a similar fashion to clinical practice guidelines published by the Endocrine Society in 2010 [64]. Frequent and serial administration of the ADAM questionnaire and sexual health inventory for men (SHIM) may be incorporated to assess treatment response.

Another OPIAD treatment option could be to cycle different opioids, to incorporate non-opioid treatments, or to avoid

long-acting opioids— there is some evidence that certain opioids may promote hypogonadism to a greater extent than others. As discussed briefly earlier, Rubinstein et al. identified a higher incidence of OPIAD in those taking long-acting (74 %) rather than short-acting (34 %) opioids (OR 4.78, 95 % CI 1.51–15.07, $p = 0.008$ after controlling for body mass index and dosage of medication), thus concluding that decreasing the prescription rate of long-acting opioids may be of benefit in preventing androgen deficiency [21]. Additionally, novel pain medications with decreased effect on gonadotropins may hold promise. Tapentadol, a combined μ-receptor agonist and norepinephrine reuptake inhibitor, was recently shown to decrease testosterone to a lesser extent than pure μ-receptor agonists although the study was limited in that serum hormones were measured after only 6 h and their sample size appeared to be without enough power to generate statistical significance [19].

In a recent animal model, Moradi et al. studied the efficacy of pentoxifylline on rats previously made dependent on morphine in hormonal recovery. The authors noted a strong rise in LH, FSH, and testosterone in the pentoxifylline arm compared to rats receiving sucrose + morphine, and sucrose + morphine + naltrexone ($p < 0.001$ in all cases). Rises of these respective hormones were noted to be higher in the pentoxifylline arm compared to the oral sucrose only arm although not to statistical significance [76].

Future studies may focus on comparison of different opioid regimens, testosterone therapies, and alternative treatments to preserve fertility in randomized trials with QoL outcomes measured by validated questionnaires. An alternative to traditional testosterone replacement includes clomiphene citrate (CC), a selective estrogen receptor modulator (SERM), which inhibits central estrogen feedback, and upregulates endogenous hypothalamic function leading to increased LH, FSH, and endogenous T levels as well as enhanced spermatogenesis. Although clomiphene citrate has been studied in hypogonadal men with excellent efficacy and minimal side effects, to our knowledge, there is one clinical trial examining clomiphene citrate therapy in the setting of OPIAD [77].

Clomiphene citrate (CC) in the setting of OPIAD may be especially beneficial for men desiring fertility preservation with simultaneous treatment of low testosterone. In the senior author's experience, excellent responses have been noted in clinical practice with improved QoL and semen analysis findings without adverse effects in men with OPIAD (Wosnitzer MS. Unpublished clinical communication. 2016.). CC is approved by the Food and Drug Administration (FDA) for treatment of ovulatory dysfunction in females desiring pregnancy and is included in the American Society Reproductive Medicine guidelines [78]. CC has not been submitted to the FDA for investigation of infertility or hypogonadism in men, and subsequently is not FDA-approved for these indications. CC, however, has been incorporated into urologic clinical practice for treatment of these conditions, with demonstrated biochemical and clinical efficacy for the treatment of hypogonadism and avoidance of the negative effects on the hypothalamic-pituitary-gonadal (HPG) axis (decreased GnRH, LH, FSH), which characterize exogenous testosterone therapy [79–85]. Given suppression of the HPG axis in OPIAD, clomiphene citrate is a logical treatment consideration. In addition, CC has positive effects with few side effects reported with low dosage utilized in men [82]. Specifically, CC has shown benefit in male infertility including oligozoospermia, and non-obstructive azoospermia [86], with potential improvement in microdissection testicular sperm extraction (micro-TESE) outcomes for non-obstructive azoospermia [87, 88] described in the literature. Follow-up monitoring for patients being treated with CC therapy is similar to that described for exogenous TRT above with baseline labs and serial 3–12-month lab follow-up testing.

Conclusion

Opioid prescribing and abuse are widespread concerns today. The use of long-acting opioids carries risks of addiction along with systemic side effects including hypogonadotropic hypogonadism (opioid-induced androgen deficiency) with significant prevalence and associated morbidity. Physicians should monitor for OPIAD and associated sequelae during opioid treatment. Patients should be educated regarding the impact that opioids may have on the endocrine system with particular emphasis on androgen deficiency and associated symptoms. Diagnosis is extrapolated from accepted society guideline thresholds for testosterone deficiency. Treatment options include testosterone replacement therapy with transdermal or injection preparations. Selective estrogenic receptor modulators (SERMs) such as clomiphene citrate may be considered as an alternative for men with fertility concerns. There is a paucity of prospective trials defining the most effective management strategies for those diagnosed with OPIAD. Available studies indicate that testosterone replacement therapy is effective and safe in studies of men with OPIAD. In addition to OPIAD treatment, alternatives to opioid medication, including NSAIDs, novel agents, or medication reduction, should be incorporated into pain management regimens when feasible. Larger prospective, randomized, double-blinded and placebo-controlled studies should be undertaken in an effort to develop potential consensus criteria for OPIAD diagnosis and management. These studies should implement validated questionnaires to address baseline and post-intervention outcomes related to quality of life, sexual desire, erectile function, libido, fertility, and pain perception. A multidisciplinary care team is the optimal approach for OPIAD management.

Compliance with Ethical Standards

Conflict of Interest Timothy K. O'Rourke, Jr. and Matthew S. Wosnitzer each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. J Pain. 2002;3(5):377–84.
2. Cicero TJ. Opiate and opioid modulation of reproductive endocrinology in the male and female: development and pregestational aspects. NIDA Res Monogr. 1984;55:14–23.
3. Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. Exp Clin Psychopharmacol. 2008;16(5):405–16. doi:10.1037/a0013628.
4. Schug SA, Zech D, Grond S. Adverse effects of systemic opioid analgesics. Drug Saf. 1992;7(3):200–13.
5. Haddox J, Joransen DE, Angarola RT. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain. 1997;13(1):6–8.
6. Azizi F, Vagenakis AG, Longcope C, Ingbar SH, Braverman LE. Decreased serum testosterone concentration in male heroin and methadone addicts. Steroids. 1973;22(4):467–72.
7. Katz N, Mazer NA. The impact of opioids on the endocrine system. Clin J Pain. 2009;25(2):170–5. doi:10.1097/AJP.0b013e3181850df6.
8. Aloisi AM, Pari G, Ceccarelli I, Vecchi I, Ietta F, Lodi L, et al. Gender-related effects of chronic non-malignant pain and opioid therapy on plasma levels of macrophage migration inhibitory factor (MIF). Pain. 2005;115(1-2):142–51. doi:10.1016/j.pain.2005.02.019.
9. Abs R, Verhelst J, Maeyaert J, Van Buyten JP, Opsomer F, Adriaensen H, et al. Endocrine consequences of long-term intrathecal administration of opioids. J Clin Endocrinol Metab. 2000;85(6):2215–22. doi:10.1210/jcem.85.6.6615.
10. Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer. 2004;100(4):851–8. doi:10.1002/cncr.20028.
11. Birthi P, Nagar VR, Nickerson R, Sloan PA. Hypogonadism associated with long-term opioid therapy: a systematic review. J Opioid Manage. 2015;11(3):255–78. doi:10.5055/jom.2015.0274.
12. Woody G, McLellan AT, O'Brien C, Persky H, Stevens G, Arndt I, et al. Hormone secretion in methadone-dependent and abstinent patients. NIDA Res Monogr. 1988;81:216–23.
13. Ceccarelli I, De Padova AM, Fiorenzani P, Massafra C, Aloisi AM. Single opioid administration modifies gonadal steroids in both the CNS and plasma of male rats. Neuroscience. 2006;140(3):929–37. doi:10.1016/j.neuroscience.2006.02.044.
14. McDonald JP, Torrey AJ, Mehta MP, Delima LG. Beyond respiratory depression and constipation: adverse effects of opioids. J Miss State Med Assoc. 2015;56(7):193–5.
15. Gudin JA, Laitman A, Nalamachu S. Opioid related endocrinopathy. Pain Med. 2015;16 Suppl 1:S9–15. doi:10.1111/pme.12926.
16. Lundh D, Hedelin H, Jonsson K, Gifford M, Larsson D. Assessing chronic pelvic pain syndrome patients: blood plasma factors and cortisol saliva. Scand J Urol. 2013;47(6):521–8. doi:10.3109/21681805.2013.769460.
17. Forman LJ, Tingle V, Estilow S, Cater J. The response to analgesia testing is affected by gonadal steroids in the rat. Life Sci. 1989;45(5):447–54.
18. Carullo V, Fitz-James I, Delphin E. Opioid-induced hyperalgesia: a diagnostic dilemma. J Pain Palliat Care Pharmacother. 2015;29(4):378–84. doi:10.3109/15360288.2015.1082006.
19. Eichenbaum G, Gohler K, Etropolski M, Steigerwald I, Pergolizzi J, Kim M, et al. Does tapentadol affect sex hormone concentrations differently from morphine and oxycodone? An initial assessment and possible implications for opioid-induced androgen deficiency. J Opioid Manage. 2015;11(3):211–27. doi:10.5055/jom.2015.0270.
20. Bawor M, Bami H, Dennis BB, Plater C, Worster A, Varenbut M, et al. Testosterone suppression in opioid users: a systematic review and meta-analysis. Drug Alcohol Depend. 2015;149:1–9. doi:10.1016/j.drugalcdep.2015.01.038.
21. 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(10):840–5. doi:10.1097/AJP.0b013e31827c7b5d.
22. Rubinstein A, Carpenter DM. Elucidating risk factors for androgen deficiency associated with daily opioid use. Am J Med. 2014;127(12):1195–201. doi:10.1016/j.amjmed.2014.07.015.
23. McCarthy M. Opioids should be last resort to treat chronic pain, says draft CDC guideline. BMJ. 2015;351:h6905. doi:10.1136/bmj.h6905.
24. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. MMWR Recomm Rep. 2016;65(1):1–49. doi:10.15585/mmwr.rr6501e1.
25. Elliott JA, Horton E, Fibuch EE. The endocrine effects of long-term oral opioid therapy: a case report and review of the literature. J Opioid Manag. 2011;7(2):145–54.
26. Morley JE. The endocrinology of the opiates and opioid peptides. Metab Clin Exp. 1981;30(2):195–209.
27. Paice JA, Penn RD, Ryan WG. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. J Pain Symptom Manag. 1994;9(2):126–31.
28. Cicero TJ, Schainker BA, Meyer ER. Endogenous opioids participate in the regulation of the hypothalamus-pituitary-luteinizing hormone axis and testosterone's negative feedback control of luteinizing hormone. Endocrinology. 1979;104(5):1286–91. doi:10.1210/endo-104-5-1286.
29. Giri M, Kaufman JM. Opioidergic modulation of in vitro pulsatile gonadotropin-releasing hormone release from the isolated medial basal hypothalamus of the male guinea pig. Endocrinology. 1994;135(5):2137–43. doi:10.1210/endo.135.5.7956937.
30. Graves GR, Kennedy TG, Weick RF, Casper RF. The effect of nalmefene on pulsatile secretion of luteinizing hormone and prolactin in men. Hum Reprod. 1993;8(10):1598–603.
31. Veldhuis JD, Rogol AD, Samojlik E, Ertel NH. Role of endogenous opiates in the expression of negative feedback actions of androgen and estrogen on pulsatile properties of luteinizing hormone secretion in man. J Clin Invest. 1984;74(1):47–55. doi:10.1172/jci111417.
32. Pende A, Musso NR, Montaldi ML, Pastorino G, Arzese M, Devilla L. Evaluation of the effects induced by four opiate drugs, with different affinities to opioid receptor subtypes, on anterior pituitary LH, TSH, PRL and GH secretion and on cortisol secretion in normal men. Biomed Pharmacother. 1986;40(5):178–82.

33. Andersson KE, Wagner G. Physiology of penile erection. Physiol Rev. 1995;75(1):191–236.
34. Melis MR, Succu S, Spano MS, Argiolas A. Morphine injected into the paraventricular nucleus of the hypothalamus prevents noncontact penile erections and impairs copulation: involvement of nitric oxide. Eur J Neurosci. 1999;11(6):1857–64.
35. Melis MR, Succu S, Iannucci U, Argiolas A. Prevention by morphine of apomorphine- and oxytocin-induced penile erection and yawning: involvement of nitric oxide. Naunyn Schmiedeberg's Arch Pharmacol. 1997;355(5):595–600.
36. Daniell HW. DHEAS deficiency during consumption of sustained-action prescribed opioids: evidence for opioid-induced inhibition of adrenal androgen production. J Pain. 2006;7(12):901–7. doi:10.1016/j.jpain.2006.04.011.
37. Brennan MJ. The effect of opioid therapy on endocrine function. Am J Med. 2013;126(3 Suppl 1):S12–8. doi:10.1016/j.amjmed.2012.12.001.
38. Allolio B, Schulte HM, Deuss U, Kallabis D, Hamel E, Winkelman W. Effect of oral morphine and naloxone on pituitary-adrenal response in man induced by human corticotropin-releasing hormone. Acta Endocrinol. 1987;114(4):509–14.
39. Delitala G, Grossman A, Besser GM. The participation of hypothalamic dopamine in morphine-induced prolactin release in man. Clin Endocrinol. 1983;19(4):437–44.
40. Devilla L, Pende A, Morgano A, Giusti M, Musso NR, Lotti G. Morphine-induced TSH release in normal and hypothyroid subjects. Neuroendocrinology. 1985;40(4):303–8.
41. Rittmaster RS, Cutler Jr GB, Sobel DO, Goldstein DS, Koppelman MC, Loriaux DL, et al. Morphine inhibits the pituitary-adrenal response to ovine corticotropin-releasing hormone in normal subjects. J Clin Endocrinol Metab. 1985;60(5):891–5. doi:10.1210/jcem-60-5-891.
42. 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(3):200–10. doi:10.1016/j.jpain.2005.10.009.
43. Adams ML, Sewing B, Forman JB, Meyer ER, Cicero TJ. Opioid-induced suppression of rat testicular function. J Pharmacol Exp Ther. 1993;266(1):323–8.
44. Kalra PS, Sahu A, Kalra SP. Opiate-induced hypersensitivity to testosterone feedback: pituitary involvement. Endocrinology. 1988;122(3):997–1003. doi:10.1210/endo-122-3-997.
45. Blank MS, Fabbri A, Catt KJ, Dufau ML. Inhibition of luteinizing hormone release by morphine and endogenous opiates in cultured pituitary cells. Endocrinology. 1986;118(5):2097–101. doi:10.1210/endo-118-5-2097.
46. Jordan D, Tafani JA, Ries C, Zajac JM, Simonnet G, Martin D, et al. Evidence for multiple opioid receptors in the human posterior pituitary. J Neuroendocrinol. 1996;8(11):883–7.
47. Agirregoitia E, Valdivia A, Carracedo A, Casis L, Gil J, Subiran N, et al. Expression and localization of delta-, kappa-, and mu-opioid receptors in human spermatozoa and implications for sperm motility. J Clin Endocrinol Metab. 2006;91(12):4969–75. doi:10.1210/jc.2006-0599.
48. Kew D, Muffly KE, Kilpatrick DL. Proenkephalin products are stored in the sperm acrosome and may function in fertilization. Proc Natl Acad Sci U S A. 1990;87(23):9143–7.
49. Davidson A, Vermesh M, Paulson RJ, Graczykowski JW, Lobo RA. Presence of immunoreactive beta-endorphin and calcitonin in human seminal plasma, and their relation to sperm physiology. Fertil Steril. 1989;51(5):878–80.
50. Agirregoitia E, Subiran N, Valdivia A, Gil J, Zubero J, Irazusta J. Regulation of human sperm motility by opioid receptors. Andrologia. 2012;44 Suppl 1:578–85. doi:10.1111/j.1439-0272.2011.01230.x.
51. Subiran N, Candenas L, Pinto FM, Cejudo-Roman A, Agirregoitia E, Irazusta J. Autocrine regulation of human sperm motility by the met-enkephalin opioid peptide. Fertil Steril. 2012;98(3):617–25.e3. doi:10.1016/j.fertnstert.2012.05.036.
52. Ragni G, De Lauretis L, Bestetti O, Sghedoni D, Gambaro V. Gonadal function in male heroin and methadone addicts. Int J Androl. 1988;11(2):93–100.
53. Safarinejad MR, Asgari SA, Farshi A, Ghaedi G, Kolahi AA, Iravani S, 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. doi:10.1016/j.reprotox.2012.11.010.
54. Vanderschueren D, Vandenput L, Boonen S, Lindberg MK, Bouillon R, Ohlsson C. Androgens and bone. Endocr Rev. 2004;25(3):389–425. doi:10.1210/er.2003-0003.
55. Perez-Castrillon JL, Olmos JM, Gomez JJ, Barrallo A, Riancho JA, Perera L, et al. Expression of opioid receptors in osteoblast-like MG-63 cells, and effects of different opioid agonists on alkaline phosphatase and osteocalcin secretion by these cells. Neuroendocrinology. 2000;72(3):187–94.
56. Irwig MS. Bone health in hypogonadal men. Curr Opin Urol. 2014;24(6):608–13. doi:10.1097/mou.0000000000000104.
57. Hannemann A, Breer S, Wallaschofski H, Nauck M, Baumeister SE, Barvencik F, et al. Osteocalcin is associated with testosterone in the general population and selected patients with bone disorders. Andrology. 2013;1(3):469–74. doi:10.1111/j.2047-2927.2012.00044.x.
58. Gotthardt F, Huber C, Thierfelder C, Grize L, Kraenzlin M, Scheidegger C, et al. Bone mineral density and its determinants in men with opioid dependence. J Bone Miner Metab. 2016. doi:10.1007/s00774-015-0732-9.
59.• Finch PM, Price LM, Pullan PT, Drummond PD. Effects of testosterone treatment on bone mineral density in hypogonadal men receiving intrathecal opioids. Pain Pract. 2015;15(4):308–13. doi:10.1111/papr.12190. **This was essentially a cross-sectional study that further informed the treatment response to TRT in those taking opioids, in this case intrathecal opioids. Of note, this study also examined BMD through DEXA, a critical outcome in hypogonadal patients**.
60.•• Basaria S, Travison TG, Alford D, Knapp PE, Teeter K, Cahalan C, et al. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. Pain. 2015;156(2):280–8. doi:10.1097/01.j.pain.0000460308.86819.aa. **This was the first double-blinded, placebo-controlled randomized control trial evaluating the effectiveness of TRT in patients with OPIAD. The authors also evaluated QoL measures concordantly with T measurements and should be commended for utilization of the International Index of Erectile Function as a validated study tool**.
61.•• Huang G, Travison T, Maggio M, Edwards RR, Basaria S. Effects of testosterone replacement on metabolic and inflammatory markers in men with opioid-induced androgen deficiency. Clin Endocrinol. 2016. doi:10.1111/cen.13049. **This was a second double-blinded, placebo-controlled randomized control trial with patients from the TAP trial included. Safety outcomes related to TRT were examined and are of vital importance as the management approach for OPIAD is further elucidated**.
62. Aloisi AM, Ceccarelli I, Carlucci M, Suman A, Sindaco G, Mameli S, et al. Hormone replacement therapy in morphine-induced hypogonadic male chronic pain patients. Reprod Biol Endocrinol. 2011;9:26. doi:10.1186/1477-7827-9-26.
63.• Blick G, Khera M, Bhattacharya RK, Nguyen D, Kushner H, Miner MM. Testosterone replacement therapy outcomes among opioid users: the Testim Registry in the United States (TRiUS). Pain Med. 2012;13(5):688–98. doi:10.1111/j.1526-4637.2012.01368.x. **This was the third single-arm study evaluating the effectiveness and utility of TRT in patients in with OPIAD**.

64. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2536–59. doi:10.1210/jc.2009-2354.
65. Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2010;7(11):3572–88. doi:10.1111/j.1743-6109.2010.02062.x.
66. Healy S, Hartman A, Gustin J. Opioid-induced androgen deficiency #284. J Palliat Med. 2014;17(11):1278–9. doi:10.1089/jpm.2014.9398.
67. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metab Clin Exp. 2000;49(9):1239–42. doi:10.1053/meta.2000.8625.
68. Heufelder AE, Saad F, Bunck MC, Gooren L. Fifty-two-week treatment with diet and exercise plus transdermal testosterone reverses the metabolic syndrome and improves glycemic control in men with newly diagnosed type 2 diabetes and subnormal plasma testosterone. J Androl. 2009;30(6):726–33. doi:10.2164/jandrol.108.007005.
69. Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014;9(1):e85805. doi:10.1371/journal.pone.0085805.
70. Seftel AD, Kathrins M, Niederberger C. Critical update of the 2010 Endocrine Society Clinical Practice Guidelines for male hypogonadism: a systematic analysis. Mayo Clin Proc. 2015;90(8):1104–15. doi:10.1016/j.mayocp.2015.06.002.
71. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. N Engl J Med. 2016;374(7):611–24. doi:10.1056/NEJMoa1506119.
72. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol. 2009;55(2):310–20. doi:10.1016/j.eururo.2008.09.024.
73. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med. 2004;350(5):482–92. doi:10.1056/NEJMra022251.
74. Goodman N, Guay A, Dandona P, Dhindsa S, Faiman C, Cunningham GR. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of testosterone and cardiovascular risk. Endocr Pract. 2015;21(9):1066–73. doi:10.4158/ep14434.ps.
75. Murphy EN, Miranda R. Doubts about treating hypogonadism due to long-term opioid use with testosterone therapy: a teachable moment. JAMA Intern Med. 2014;174(12):1892–3. doi:10.1001/jamainternmed.2014.5299.
76. Moradi M, Mahmoodi M, Raoofi A, Ghanbari A. Chorionic morphine, naltrexone and pentoxifylline effect on hypophyso-gonadal hormones of male rats. Bratisl Lek Listy. 2015;116(4):276–9.
77. Wosnitzer MS, Schlegel PN. Clomiphene citrate for the treatment of low testosterone associated with chronic opioid pain medication administration. 2013.
78. Practice Committee of the American Society for Reproductive Medicine. Use of clomiphene citrate in women. Fertil Steril. 2006;86(5 Suppl 1):S187–93. doi:10.1016/j.fertnstert.2006.08.023.
79. Shabsigh A, Kang Y, Shabsign R, Gonzalez M, Liberson G, Fisch H, et al. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. J Sex Med. 2005;2(5):716–21. doi:10.1111/j.1743-6109.2005.00075.x.
80. Tan RS, Vasudevan D. Use of clomiphene citrate to reverse premature andropause secondary to steroid abuse. Fertil Steril. 2003;79(1):203–5.
81. Guay AT, Bansal S, Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. J Clin Endocrinol Metab. 1995;80(12):3546–52. doi:10.1210/jcem.80.12.8530597.
82. Moskovic DJ, Katz DJ, Akhavan A, Park K, Mulhall JP. Clomiphene citrate is safe and effective for long-term management of hypogonadism. BJU Int. 2012;110(10):1524–8. doi:10.1111/j.1464-410X.2012.10968.x.
83. Katz DJ, Nabulsi O, Tal R, Mulhall JP. Outcomes of clomiphene citrate treatment in young hypogonadal men. BJU Int. 2012;110(4):573–8. doi:10.1111/j.1464-410X.2011.10702.x.
84. Reifsnyder JE, Ramasamy R, Husseini J, Schlegel PN. Role of optimizing testosterone before microdissection testicular sperm extraction in men with nonobstructive azoospermia. J Urol. 2012;188(2):532–6. doi:10.1016/j.juro.2012.04.002.
85. Taylor F, Levine L. Clomiphene citrate and testosterone gel replacement therapy for male hypogonadism: efficacy and treatment cost. J Sex Med. 2010;7(1 Pt 1):269–76. doi:10.1111/j.1743-6109.2009.01454.x.
86. Hussein A, Ozgok Y, Ross L, Niederberger C. Clomiphene administration for cases of nonobstructive azoospermia: a multicenter study. J Androl. 2005;26(6):787–91. doi:10.2164/jandrol.04180. discussion 92-3.
87. Hussein A, Ozgok Y, Ross L, Rao P, Niederberger C. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. BJU Int. 2013;111(3 Pt B):E110–4. doi:10.1111/j.1464-410X.2012.11485.x.
88. Ramasamy R, Ricci JA, Palermo GD, Gosden LV, Rosenwaks Z, Schlegel PN. Successful fertility treatment for Klinefelter's syndrome. J Urol. 2009;182(3):1108–13. doi:10.1016/j.juro.2009.05.019.