

# Opioid-induced androgen deficiency in men: Prevalence, pathophysiology, and efficacy of testosterone therapy

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## Abstract

**Background:** Opioid analgesics are frequently prescribed for the treatment of chronic pain and are a common cause of male androgen deficiency. Despite its high prevalence, this adverse effect of chronic opioid use remains underappreciated by clinicians. As a result, androgen deficiency remains underdiagnosed and likely undertreated. This focused review discusses the expanding literature on opioid-induced androgen deficiency and the efficacy of testosterone therapy, with a particular focus on its anti-nociceptive effects.

**Methods:** Original and review articles on opioid-induced male androgen deficiency published from 1950 through June 2024 were retrieved from PubMed using the key terms "opioids," "hypogonadism," "low testosterone," and "testosterone therapy." References within the retrieved publications were also researched.

**Results:** Opioids suppress the gonadal axis mainly by inhibiting GnRH synthesis and secretion. The prevalence of opioid-induced androgen deficiency in men varies between 20% and 80% and is influenced by the type of opioid used, duration of exposure, age of the cohort, and how low testosterone was defined. Limited data from clinical trials suggest that testosterone therapy improves libido, body composition, and certain domains of quality of life. Early evidence also suggests that testosterone has anti-nociceptive properties, confirming findings from preclinical and population studies.

**Conclusion:** Chronic opioid use is a common but underappreciated cause of androgen deficiency in men. There is a need to raise awareness among clinicians regarding this adverse effect of opioid use. Testosterone therapy could be considered in men with unequivocal androgen deficiency after a thorough clinical evaluation. Ongoing clinical trials will shed further light on the efficacy of testosterone therapy, particularly regarding its anti-nociceptive effects.

## KEYWORDS

androgen deficiency, hypogonadism, opioids, testosterone

## 1 | INTRODUCTION

Opioids have been used for their analgesic effects for thousands of years. Papyrus records dating back to 3400 BC have revealed that the Mesopotamians and ancient Egyptians cultivated *Papaver somniferum*, a species of poppy plant, and extracted opium for the treatment of pain.<sup>1,2</sup> With the advancement of modern medicine, the analgesic potency of opioids has greatly improved.<sup>3</sup> Because of their efficacy, relatively low cost, and widespread availability, the use of synthetic opioids has increased in the United States. It is estimated that approximately 5–8 million Americans are on opioid analgesics for the management of chronic pain.<sup>4</sup>

Because opioid receptors are present in various organ systems, opioid use is associated with a plethora of adverse effects, including respiratory depression, cardiac conduction disturbances, gastrointestinal dysmotility, and, paradoxically, hyperalgesia.<sup>5</sup> Opioid analgesics also impact various endocrine axes (adrenal, thyroid, growth hormone), but the hypothalamic-pituitary-gonadal (HPG) axis remains the most vulnerable to suppression.<sup>6,7</sup> Opioid-induced androgen deficiency can occur in any age group and serum testosterone concentrations often decline into the castrate range in men who are receiving chronic treatment with potent opioids.<sup>6,7</sup> Opioid-induced androgen deficiency is associated with sexual dysfunction, mood changes, low bone mass, and reduced quality of life.<sup>6,7</sup> As opioid analgesics are prescribed widely, it predisposes a large number of patients to these adverse effects. However, these side effects remain underappreciated by clinicians as data demonstrate that 76% of general practitioners and even 30% of endocrinologists are not aware of them.<sup>8</sup> Furthermore, only a few randomized double-blind, placebo-controlled trials have assessed the efficacy of testosterone replacement in men with opioid-induced androgen deficiency.

This focused review addresses the (i) pharmacology of opioids, (ii) pathophysiology, epidemiology and clinical consequences of opioid-induced androgen deficiency, and (iii) efficacy data from clinical trials of testosterone therapy in this patient population.

## 2 | OPIOIDS AND OPIOID RECEPTORS

Opioid analgesics are a class of drugs structurally related to alkaloids extracted from the resin of the opium poppy plant.<sup>1,2</sup> These natural alkaloids are referred to as opiates and include morphine, codeine, thebaine, and papaverine.<sup>2</sup> Opioids are broadly classified as endogenous or nonendogenous. The four major classes of endogenous opioids include  $\beta$ -endorphins, enkephalins, dynorphins, and the most recently discovered nociceptin (also known as orphanin FQ), and are derived from proopiomelanocortin, preproenkephalin A, preproenkephalin B, and prepronociceptin, respectively.<sup>7</sup> Nonendogenous opioids are classified as natural, semisynthetic or synthetic. Codeine and morphine are natural opioids while semisynthetic opioids include hydrocodone, oxycodone, and buprenorphine. Synthetic opioids include potent agents like fentanyl. Synthetic opioids are further divided into four main classes: morphinan (also known as the phenan-

threnes), diphenylheptane, benzomorphan, and phenylpiperidine. From a functional perspective, opioids are classified based on their affinity for opioid receptors as agonists, partial agonists, or antagonists (Table 1).

Opioid receptors are G-protein-coupled receptors. They are present in the nervous system, skin, gastrointestinal tract, and endocrine organs.<sup>2</sup> The four main types of opioid receptors are  $\mu$  ( $\mu$ ),  $\delta$  ( $\delta$ ),  $\kappa$  ( $\kappa$ ), and nociceptin (NOP).<sup>3</sup> The  $\mu$  receptors are primarily localized in the cerebral cortex, medial thalamus, and periaqueductal gray matter, and mediate effects on nociception, respiration, gastrointestinal motility, mood, and consciousness.<sup>1</sup> The  $\kappa$  receptors are concentrated in the limbic system, brain stem, and spinal cord and mediate dysphoria and spinal analgesia; these receptors are also present in the hypothalamus (median eminence) and the pituitary. The  $\delta$  receptors are primarily located in the basal ganglia and have been posited to play a role in psychomimetic and dysphoric effects.<sup>1</sup> The NOP receptors are considered atypical (nonclassical) receptors as they do not respond to naloxone (an opioid antagonist). They are expressed in various regions of the brain and their effects are currently under investigation.<sup>9</sup> The three classical opioid receptors have also been detected in gonadotropin-releasing hormone (GnRH) and kisspeptin neurons in a variety of animal species;<sup>7,10–12</sup> thus, it is not surprising that opioids have a profound impact on the HPG axis.

## 3 | MECHANISMS BEHIND OPIOID-INDUCED ANDROGEN DEFICIENCY

Opioid analgesics potently suppress the HPG axis which occurs via a central effect on the hypothalamus (secondary hypogonadism). This effect is mediated via two main mechanisms: i) direct inhibition of GnRH synthesis and secretion and ii) indirect effect via hyperprolactinemia (Figure 1).<sup>13</sup> Although the predominant mechanism by which opioids induce androgen deficiency is suppression of GnRH, some reports suggest that opioids may reduce testosterone secretion by direct action on the testes.<sup>6,7</sup>

### 3.1 | Inhibition of GnRH synthesis and secretion

A considerable body of preclinical and clinical data suggests that opioids suppress the HPG axis by inhibiting the synthesis and secretion of GnRH from the hypothalamus.<sup>14</sup> Opioid analgesics bind to the opioid receptors in the hypothalamus and downregulate GnRH mRNA levels, resulting in reduced secretion of gonadotropins from the anterior pituitary.<sup>15,16</sup> Indeed, both endogenous and nonendogenous opioids attenuate GnRH and luteinizing hormone (LH) pulsatility, and administration of naloxone increases both pulse amplitude and pulse frequency of LH.<sup>17</sup> Preclinical research on the regulation of GnRH mRNA in rat brains using in situ hybridization has shown that treatment with morphine for only a period of 4 days reduced GnRH mRNA levels, an effect that was reversed by naloxone, further confirming

**TABLE 1** Summary of various opioids and their relative affinities toward opioid receptors.

Type	Class	Opioid	Source	Receptor			
				$\mu$	$\delta$	$\kappa$	NOP
Endogenous		$\beta$ -endorphin		↑↑↑↑	↑↑	↑↑	∅
		Enkephalin		↑↑	↑↑↑	∅	∅
		Dynorphin		↑↑	∅	↑↑↑	∅
		Nociceptin/orphanin		∅	∅	∅	↑↑↑↑
Nonendogenous	Morphinan	Oxymorphone	Semisynthetic	↑↑↑↑	↑	↑	∅
		Hydrocodone	Semisynthetic	↑↑↑	↑↑	↑	∅
		Hydromorphone	Semisynthetic	↑↑↑	↑	↑↑	∅
		Diamorphine (Heroin)	Semisynthetic	↑↑↑	↑	∅	∅
		Morphine	Natural	↑↑↑	∅	↑	∅
		Levorphanol	Synthetic	↑↑↑	↑	↑↑	∅
		Oxycodone	Semisynthetic	↑↑	∅	↑	∅
		Codeine	Natural	↑	↑	↑	∅
		Buprenorphine	Semisynthetic	±	X	X	±
	Diphenylheptane	Methadone	Synthetic	↑↑↑	∅	∅	∅
		Propoxyphene	Synthetic	↑	∅	↑	∅
	Benzomorphan	Pentazocine	Synthetic	X	∅	↑↑↑	∅
	Phenylpiperidine	Fentanyl	Synthetic	↑↑↑	∅	↑	∅
		Sufentanil	Synthetic	↑↑↑	∅	∅	∅
		Meperidine	Synthetic	↑↑	↑	↑	∅
	Cyclohexanol	Tramadol	Synthetic	↑↑	↑	↑	∅
	Benzenoid	Tapentadol	Synthetic	↑↑	↑	↑	∅

Note: ↑↑↑↑, extreme affinity; ↑↑↑, high affinity; ↑↑, intermediate affinity; ↑, weak affinity; ∅, no affinity; X, antagonist; ±, partial agonist. Data summarized from Refs. 1–3, 7, and 9.

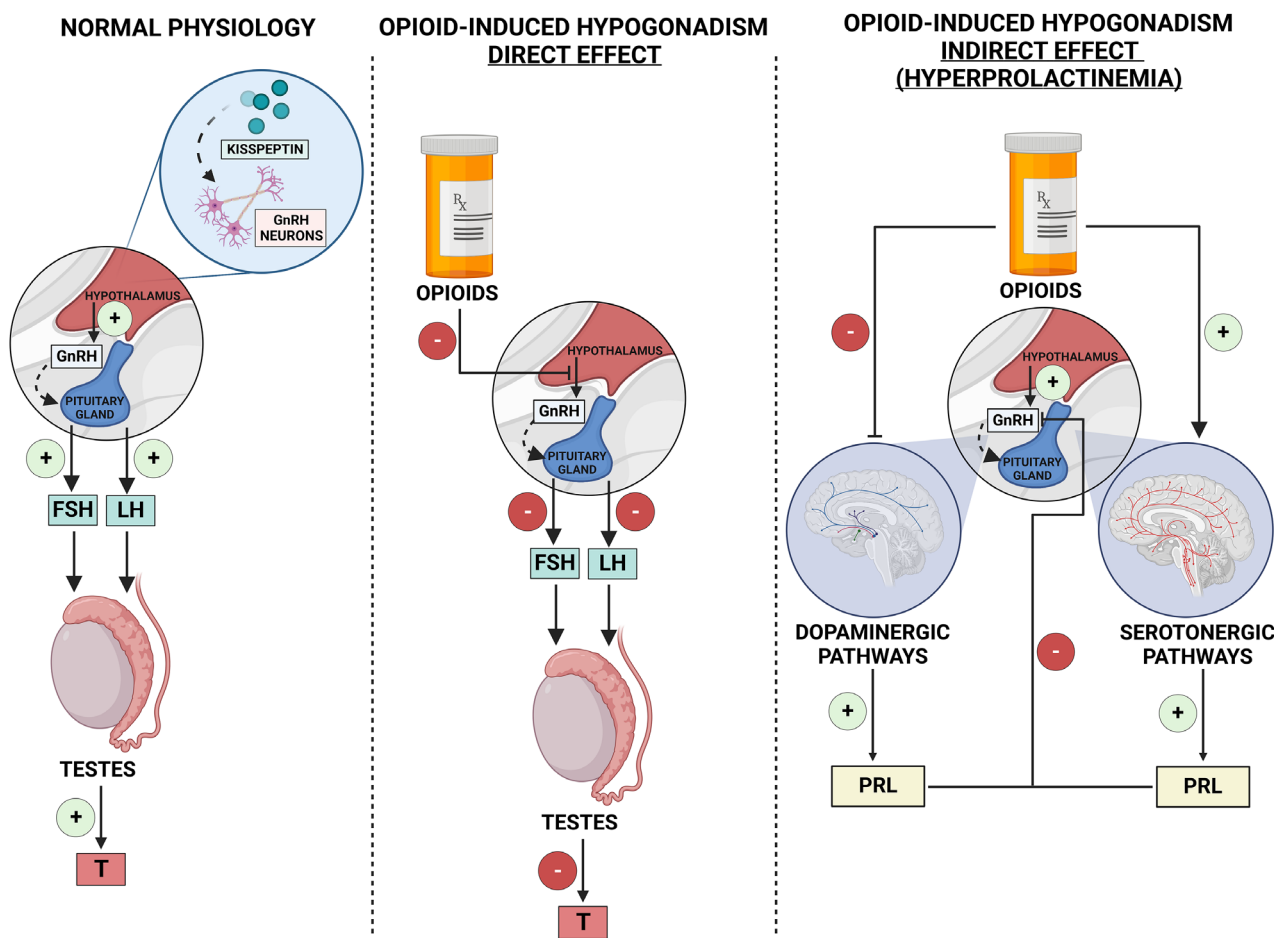
Abbreviations:  $\mu$ , mu;  $\delta$ , delta;  $\kappa$ , kappa; NOP, nociceptin.

that reduced GnRH synthesis is likely the main mechanism by which opioids suppress the HPG axis.<sup>7,18</sup> In human studies, administration of naltrexone to healthy men not taking opioids also increases LH pulsatility. These data provide evidence that endogenous opioid tone attenuates the activity of the HPG axis.<sup>19</sup>

### 3.2 | Hyperprolactinemia

In addition to direct suppression of GnRH synthesis and secretion, opioids also suppress the HPG axis indirectly by causing hyperprolactinemia.<sup>16</sup> Opioid administration can lead to an acute elevation in serum prolactin levels, which is reversed by dopamine agonists. In male rats, short-term treatment with morphine increases

prolactin mRNA levels in the pituitary, an effect that is attenuated by concomitant administration of naloxone.<sup>20</sup> In a cross-sectional study, serum prolactin concentrations in men with a history of addiction to heroin were higher ( $12.3 \pm 10.5$  ng/mL) than in controls ( $5.9 \pm 2.5$  ng/mL), though they were still in the normal range.<sup>21</sup> Data from human studies suggest that the effects of chronic opioid use on serum prolactin levels have been variable.<sup>22–24</sup> Although the exact mechanism by which opioids increase serum prolactin concentrations remains unclear, it has been posited that chronic stimulation of the  $\mu$  opioid receptor inhibits dopaminergic pathways with ensuing increase in prolactin secretion.<sup>25</sup> Some studies have also suggested that stimulation of serotonergic pathways by opioid analgesics may lead to elevation in prolactin.<sup>26,27</sup> In a recent meta-analysis of seven studies of patients who were taking opioid analgesics, serum



**FIGURE 1** Direct and indirect mechanisms by which opioids cause hypogonadism. +, stimulation; -, inhibition; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PRL, prolactin; T, testosterone.

prolactin concentrations were found to be elevated in four of these studies.<sup>28</sup>

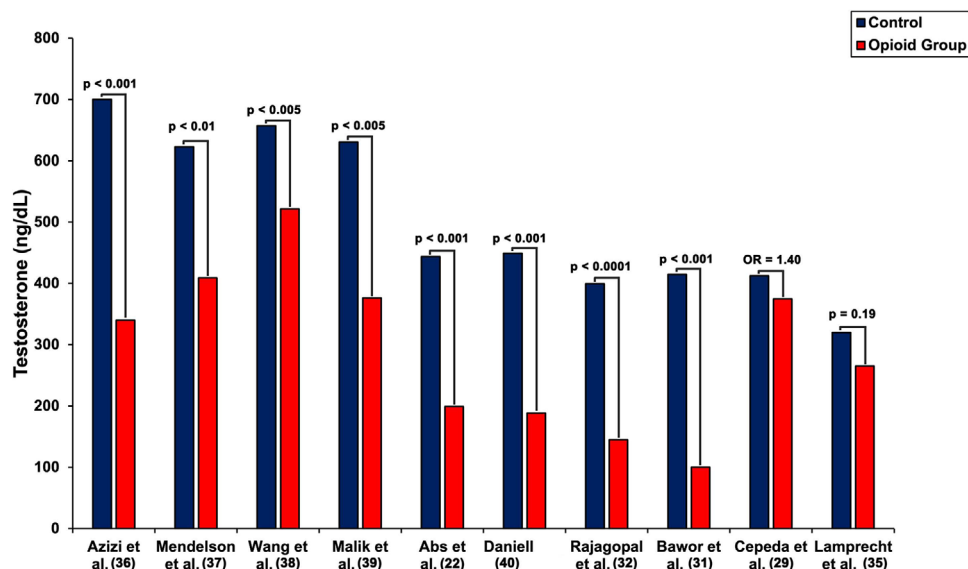
#### 4 | EPIDEMIOLOGY OF OPIOID-INDUCED ANDROGEN DEFICIENCY

The prevalence of opioid-induced androgen deficiency in men has been reported to range between 20–80% depending on the population studied, type of opioid used, age of the cohort, and testosterone thresholds used to define low testosterone levels.<sup>16</sup> A recent systematic review and meta-analysis reported that ~70% of men on chronic opioids are androgen deficient.<sup>28</sup> In a cross-sectional study, participants >70 years of age had higher odds (odds ratio [OR] 1.7) of having low testosterone compared with participants between 17 and 45 years of age (OR 1.4) after controlling for opioid use.<sup>29</sup> Although men across all age groups may be affected, men 50 years and older with medical comorbidities are more prone to developing opioid-induced androgen deficiency.<sup>30</sup>

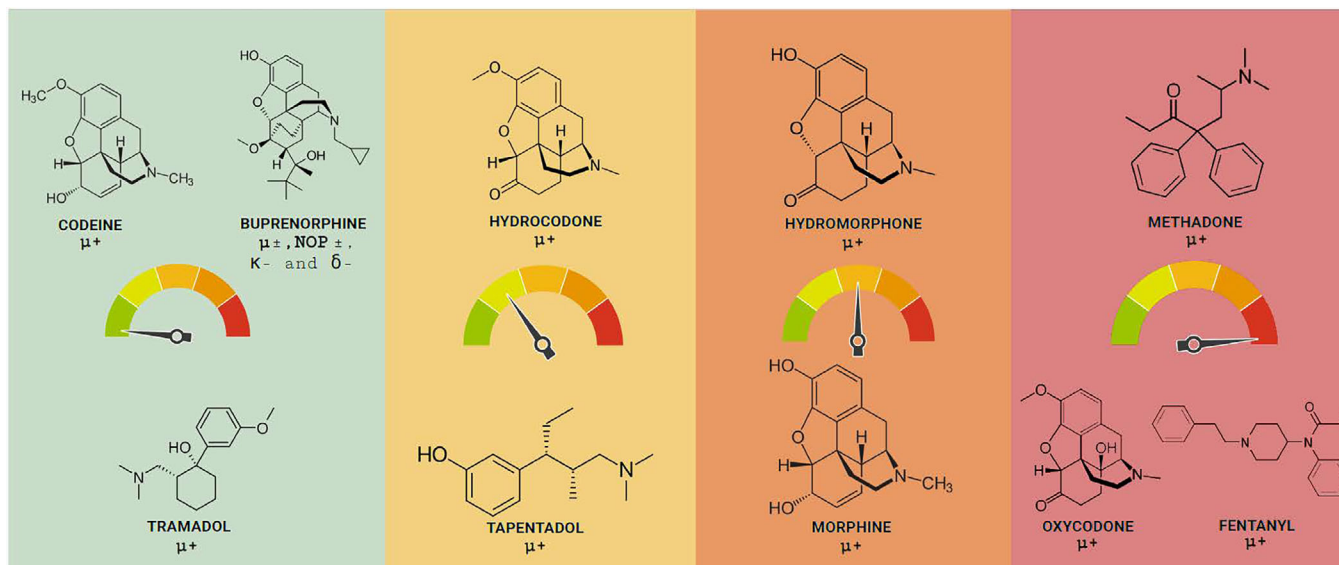
Over the past five decades, many studies have assessed the effects of opioids on the HPG axis.<sup>22,31–40</sup> Earlier studies showed that men who were prescribed high-dose methadone to treat opioid addiction

had lower serum testosterone concentrations compared with age-matched controls.<sup>36,37</sup> Similarly, mean serum testosterone concentrations are lower in men with heroin addiction ( $376.30 \pm 37.59$  ng/dL) than in healthy controls ( $630.36 \pm 23.31$  ng/dL).<sup>38</sup> In a large meta-analysis of > 3000 patients receiving chronic opioids, low testosterone levels were seen in 63% of men.<sup>28</sup> Although opioids administered via any route can suppress the HPG axis, intrathecal opioids are most potent in suppressing testosterone levels.<sup>22</sup> Patients receiving fentanyl (OR 25.73), methadone (OR 7.33) or oxycodone (OR 3.15) have greater odds of having low testosterone compared with those receiving hydrocodone.<sup>30,41</sup> Similarly, patients on long-acting opioids have greater odds (OR 3.39) of developing androgen deficiency.<sup>42</sup> Some of the observational studies that assessed endogenous testosterone concentrations in men on opioids are summarized in Figure 2.

The extent to which opioids suppress the HPG axis also depends on the dose and pharmacology of the opioid.<sup>43</sup> Doses exceeding 100 mg of morphine equivalents are more likely to result in androgen deficiency, likely due to sustained inhibition of the HPG axis. Similarly,  $\mu$  opioid agonists, such as fentanyl and methadone, are more likely to suppress the HPG axis compared with partial  $\mu$  agonists (such as buprenorphine and tapentadol)<sup>44,45</sup> (Figure 3).



**FIGURE 2** Summary of results from observational studies assessing serum testosterone concentrations in men on opioid analgesics versus controls. OR, odds ratio. In Cepeda et al.<sup>29</sup> (OR 1.40), 95% CI was 1.07–1.84.



**FIGURE 3** Illustration of the potency of various opioids in suppressing the HPG axis. +, agonist; -, antagonist;  $\pm$ , partial agonist,  $\delta$ , delta;  $\kappa$ , kappa;  $\mu$ , mu; NOP, nociception.

Testosterone levels may recover after dose reduction or withdrawal of the opioid, although the time course for this recovery is variable.

Despite the high prevalence of opioid-induced androgen deficiency, this problem remains under recognized by the clinicians. A large commercial insurance database study evaluated >50,000 adult men without a prior history of androgen deficiency who were prescribed opioids for at least 90 days in a single 12-month period and compared them with a similar number of men who were prescribed opioids for 14 or fewer days.<sup>46</sup> The investigators found that, over a 5-year period, 17% of men on long-term opioids were screened for

testosterone levels, 9% were diagnosed with androgen deficiency, and only 5.76% received testosterone therapy. These data suggest that increased awareness is needed among clinicians to recognize this condition.

## 5 | CLINICAL CONSEQUENCES OF OPIOID-INDUCED ANDROGEN DEFICIENCY

Androgen deficiency resulting from opioid use affects various organ systems.<sup>47</sup> Some of these clinical consequences are summarized below.



## 5.1 | Sexual function

Testosterone is essential for male sexual function and maintenance of secondary sexual characteristics. Thus, not surprisingly, men with opioid-induced androgen deficiency experience sexual dysfunction, including erectile dysfunction, reduced libido, and dissatisfaction with sex life.<sup>48–50</sup> As methadone is a more potent suppressor of the HPG axis than buprenorphine, one study showed that men treated with methadone experience greater frequency of sexual dysfunction compared with those treated with buprenorphine.<sup>45</sup>

## 5.2 | Pain perception and tolerance

Evidence from preclinical and population studies demonstrates that testosterone modulates pain sensitivity and has anti-nociceptive properties.<sup>6</sup> For instance, castrated male mice manifest increased pain sensitivity to noxious stimuli (chemical and thermal stimuli) compared to mice with intact gonads, while administration of testosterone improves pain tolerance to these stimuli.<sup>51</sup> Studies reporting sexual dimorphism in pain perception further consolidates the anti-nociceptive action of testosterone. Indeed, a substantial body of evidence from population studies has shown that men and women do not experience pain analogously, and the prevalence of both acute and chronic pain is higher among women. A population-based survey showed that 38% of women endorsed experiencing some kind of pain the day before the survey was conducted compared with only 21% of men.<sup>52</sup> Similarly, more women report persistent pain after knee arthroscopic procedures than men, further supporting the sexual dimorphism in pain perception and tolerance.<sup>53</sup> As with clinical pain, women also display increased sensitivity to experimental pain in response to mechanical, thermal, and pressure stimuli, suggesting that higher endogenous testosterone levels in men have anti-nociceptive properties.<sup>6</sup> Neuroimaging studies have also revealed that men display unique pain processing mechanisms via activation of the rostral ventromedial medulla, which, in turn, amplifies the activity of descending pain inhibitory pathways, and activation of these pathways is positively correlated with endogenous serum testosterone concentrations.<sup>54,55</sup> Thus, suppression of endogenous testosterone in men as a consequence of opioid use negates its anti-nociceptive benefits which might lead to requirements of even higher doses of opioids to control the same magnitude of pain.

## 5.3 | Bone mineral density

Opioid use can result in low bone density by both *direct* and *indirect* mechanisms. Opioids act *directly* on osteoblasts and suppress their activity, which is manifested by reduced serum levels of osteocalcin.<sup>56</sup> Limited data also suggest that opioids impair bone healing. Opioids also reduce bone mass *indirectly* via suppression of the HPG axis as both testosterone, and its active metabolite estrogen, have anabolic

effects on the skeleton. The prevalence of low bone mass in men on opioids (both in patients on prescription opioids and in those with opioid addiction) ranges between 20% and 50% across a wide age range and is associated with lower serum testosterone levels,<sup>57–60</sup> predisposing these patients to a higher risk of fracture compared with men not on opioids.<sup>58,61</sup>

## 5.4 | Quality of life and mood

Clinical evidence suggests that testosterone possesses anxiolytic and antidepressant effects.<sup>62</sup> Compared to eugonadal men, men with androgen deficiency have a higher prevalence of dysthymia and mood disorders, which negatively affects their quality of life.<sup>63</sup> Thus, not only opioids play a role in mood changes by direct action on the central nervous system but also via reducing testosterone levels.<sup>40</sup> Data also suggest a dose-response relationship between the dose and duration of opioid use with dysthymia.<sup>64,65</sup>

# 6 | CLINICAL EVALUATION OF MEN WITH OPIOID-INDUCED ANDROGEN DEFICIENCY

Considering that opioids potently suppress the HPG axis, patients receiving long-term treatment with opioid analgesics should be informed regarding this potential side effect. Clinicians may also consider treating patients with buprenorphine, which has less suppressive effect on the HPG axis. For patients who are already on treatment with opioids for 3–6 months, it is prudent for clinicians to assess signs and symptoms of androgen deficiency and measure serum testosterone, gonadotropins, and prolactin levels. The majority of men with low testosterone levels due to opioid use will have a biochemical profile that will be consistent with central hypogonadism, that is, low serum testosterone concentrations along with low or inappropriately normal gonadotropin levels. Even if the diagnosis of opioid-induced hypogonadism seems obvious, it should be considered a diagnosis of exclusion, that is, organic hypogonadism should be excluded prior to attributing low testosterone levels solely to opioid use. Implementing this strategy will prevent missing a serious and potentially treatable condition (e.g., a pituitary lesion or an infiltrative disease). Magnetic resonance imaging of the sella in patients with a biochemical profile of secondary hypogonadism may be appropriate on a case-by-case basis. We suggest that clinicians follow published clinical practice guidelines from scientific organizations on the diagnosis and management of androgen deficiency.<sup>47</sup> If opioid-induced androgen deficiency is the final diagnosis, testosterone therapy should be considered in a symptomatic patient.

On the other hand, if hyperprolactinemia is present and deemed to be induced by opioids (after sellar imaging has excluded pituitary lesion or compression of the infundibulum), either administration of a dopamine agonist or testosterone replacement could be considered in a symptomatic patient.

**TABLE 2** Summary of studies evaluating the effects of testosterone therapy in men with opioid-induced hypogonadism.

Publication	Study design	N*	Study duration (weeks)	Sexual function	Body composition	QoL	Mood	Pain
Aloisi et al. <sup>68</sup>	Observational, prospective	17	52	+	NR	+	↔	+
Blick et al. <sup>69</sup>	Observational, prospective	90	52	+	↔	NR	+	+
Raheem et al. <sup>70</sup>	Retrospective, pilot	11	78	+	NR	NR	NR	+
Daniell et al. <sup>66</sup>	Open-label, pilot	23	24	+	NR	+	+	+
Basaria et al. <sup>6</sup>	RCT, placebo-controlled	43	14	+	+	+	NR	+
Glintborg et al. <sup>67</sup>	RCT, placebo-controlled	20	24	+	+	↔	NR	↔

Abbreviations: +, improved/increased; ↔, no change; NR, not reported; QoL, quality of life; RCT, randomized controlled trial.

\*Sample represents men on testosterone.

\*\*Some aspects improved significantly.

## 7 | EFFICACY OF TESTOSTERONE THERAPY IN OPIOID-INDUCED ANDROGEN DEFICIENCY

Although the long-term benefits of testosterone replacement in men with opioid-induced androgen deficiency are still under investigation, short-term studies have reported its efficacy on sexual function, body composition, quality of life, and nociception<sup>6,66–70</sup> (Table 2). However, only two randomized, double-blind, placebo-controlled trials of testosterone replacement in men with opioid-induced androgen deficiency have been performed to date.<sup>6,67</sup> The following section summarizes the efficacy of testosterone replacement in this patient population.

### 7.1 | Sexual function

Retrospective reports, open-label intervention studies and randomized trials have all shown that testosterone therapy improves sexual function in men with opioid-induced androgen deficiency. Although at first glance, this observation may seem mundane considering that testosterone therapy has been shown to improve sexual function in men with androgen deficiency due to other etiologies, this is still an important observation considering the direct depressive effects of opioids on the central nervous system. Observational studies show that testosterone replacement in these men improves libido and erectile function.<sup>68–70</sup> A 24-week, open-label, pilot trial of transdermal testosterone patch in men with opioid-induced androgen deficiency showed improvement in sexual function.<sup>66</sup>

The Testosterone and Pain (TAP) trial, the first double-blind, randomized, placebo-controlled trial designed to assess the efficacy of testosterone therapy in men with opioid-induced androgen deficiency, reported that men randomized to testosterone experienced greater improvement in libido compared with those randomized to placebo, although no improvement in erectile function was observed<sup>6</sup> (Figure 4A). A recent placebo-controlled trial by Glintborg et al. reported improvement in erectile function and overall sexual activity in men randomized to testosterone.<sup>67</sup>

### 7.2 | Body composition

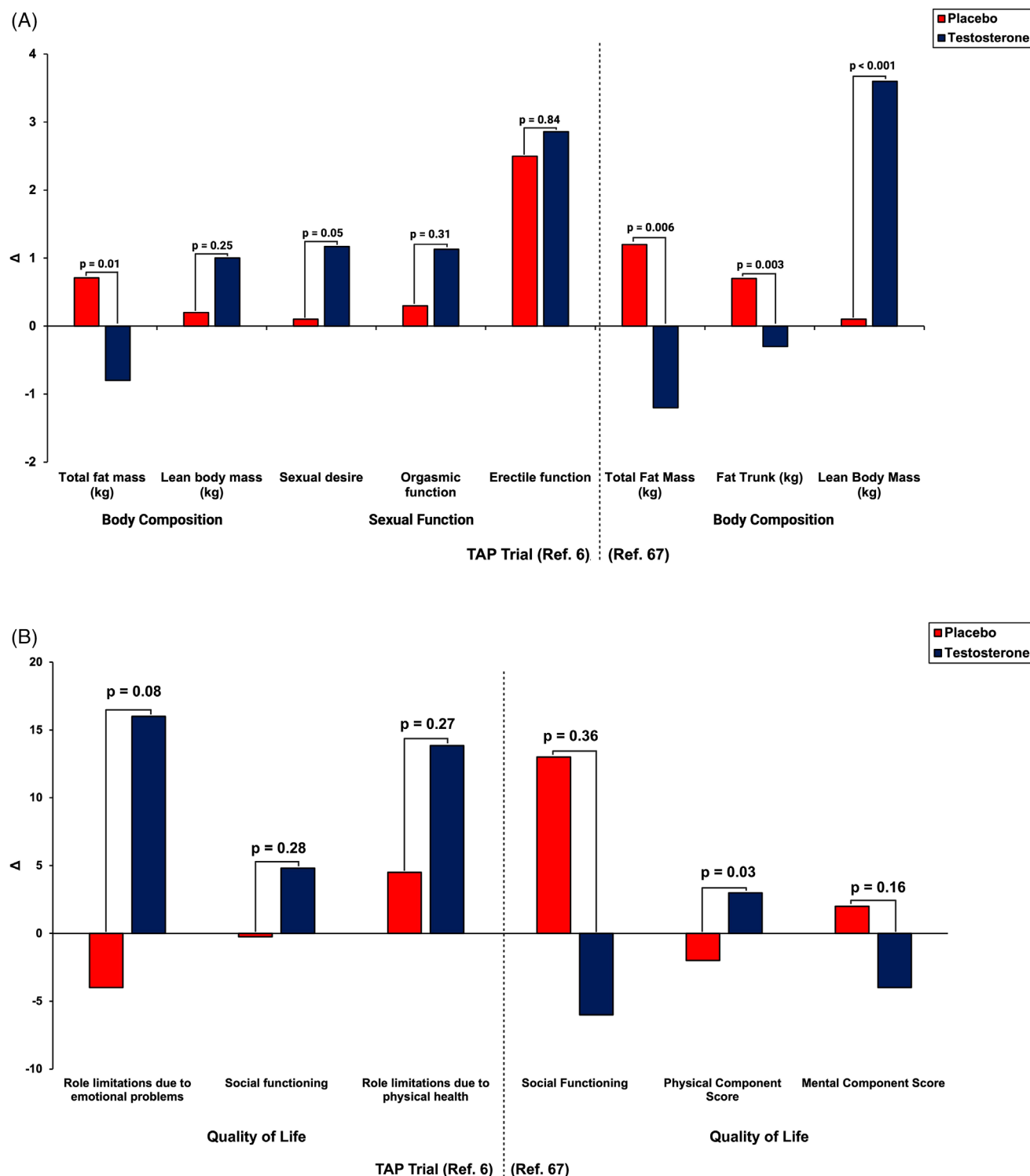
Few studies have assessed the effect of testosterone replacement on body composition in men with opioid-induced androgen deficiency. A prospective registry study that followed men on opioids who were prescribed testosterone therapy by their doctors in outpatient clinics observed no meaningful change in body composition.<sup>69</sup> In the TAP trial, men randomized to transdermal testosterone gel lost ~1.0 kg of fat mass and gained 1.0 kg of lean mass over 14 weeks of intervention<sup>6</sup> (Figure 4A). Serum biomarkers of metabolism and inflammation did not worsen during intervention.<sup>71</sup> Likewise, in their 24-week trial, Glintborg et al. reported that men randomized to testosterone undecanoate injections experienced a reduction of 1.2 kg in fat mass and an increase of 3.6 kg in lean mass<sup>67</sup> (Figure 4A). Thus, testosterone therapy in men with opioid-induced androgen deficiency leads to favorable changes in body composition.

### 7.3 | Quality of life and mood

Both observational studies and clinical trials have assessed the effects of testosterone therapy on the quality of life and mood in men with opioid-induced androgen deficiency. A prospective observational study reported improvements in mood after 12 months of testosterone therapy, and these changes correlated with circulating serum total testosterone concentrations.<sup>69</sup> Another study showed improvement in the emotional aspect of quality of life after a year of testosterone therapy.<sup>68</sup> An open-label trial with transdermal testosterone patch also demonstrated improvement in both mood and depression scores compared to baseline.<sup>66</sup> In the TAP trial, men randomized to testosterone experienced a trend toward improvement in emotional aspects of quality of life, however, social function or physical health did not improve.<sup>6</sup> Another trial demonstrated modest improvements in physical health<sup>67</sup> (Figure 4B).

### 7.4 | Pain perception and tolerance

Based on the data from preclinical and population studies, there has been substantial interest in exploring the anti-nociceptive effects of

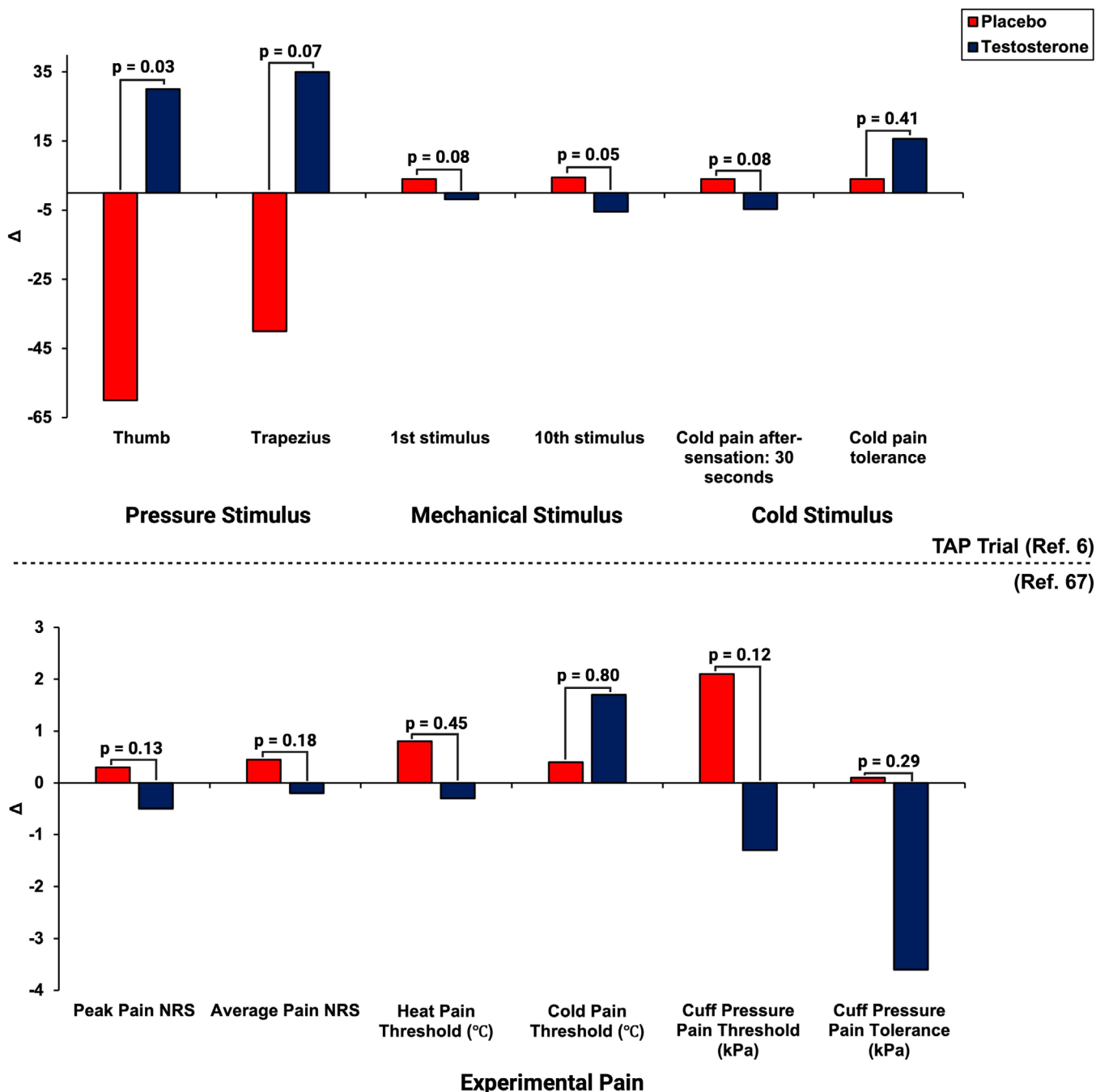


**FIGURE 4** (A) Changes in body composition and sexual function and (B) changes in quality of life in the testosterone and placebo groups in the two randomized trials of opioid-induced hypogonadism.

testosterone therapy in men on chronic opioids, particularly on its impact on pain perception and pain tolerance. In a prospective observational study of testosterone therapy, men who were taking morphine for pain management experienced improvement in clinical pain as assessed by pain questionnaires.<sup>68</sup> A retrospective study also showed

that testosterone therapy was associated with a reduction in the intensity of pain experienced by these patients.<sup>70</sup> These findings were further confirmed in an open-label trial that reported improvement in pain scores, assessed with the Brief Pain Inventory (BPI) questionnaire, in men treated with transdermal testosterone patch.<sup>66</sup> The TAP trial also





**FIGURE 5** Changes in pain perception and tolerance in the testosterone and placebo groups in the two randomized trials. NRS, numerical rating scale.

demonstrated a trend toward reduction in the pain interference score on the BPI questionnaire in men randomized to testosterone.<sup>6</sup> The TAP trial was unique in design, as in addition to assessing clinical pain, it also assessed experimental pain by conducting quantitative sensory testing procedures during which various noxious stimuli (mechanical pressure, heat stimulus, ice water hand immersion) were applied. Men randomized to testosterone demonstrated improvements in pressure pain thresholds while trends toward improvement in mechanical and thermal pain were also demonstrated.<sup>6</sup> There was no improvement in either

pain catastrophizing or sleep quality in men randomized to testosterone therapy.<sup>72</sup> In contrast, the trial by Glintborg et al. did not show improvements in either clinical or experimental pain in men randomized to testosterone<sup>67</sup> (Figure 5). Although some studies have reported reduction in the opioid dose in men who have received testosterone therapy,<sup>69,70</sup> the above-mentioned trials did not observe significant reduction in the average daily dose of opioids among men randomized to testosterone.<sup>6,67</sup> The ongoing PATH (Pain Alleviation with Testosterone in Opioid-Induced Hypogonadism) Trial (NCT04798469), a

24-week double-blind, randomized, placebo-controlled study which is being conducted by the authors, will shed further light on both the efficacy and underlying mechanisms of the anti-nociceptive effect of testosterone therapy in men on chronic opioids.

## 7.5 | Fractures and anemia

Androgen deficiency of any etiology is associated with anemia and low bone mass. A large cohort study from the Veterans Health Administration system<sup>73</sup> evaluated health outcomes of testosterone therapy in men with opioid-induced androgen deficiency. The investigators compared 14,121 men with opioid-induced androgen deficiency who were prescribed testosterone therapy with 7151 men who did not receive testosterone therapy. Men who received testosterone had lower incidence of hip fractures (hazard ratio [HR] = 0.68) and diagnosis of anemia (HR = 0.73) during a 6-year follow-up period. These findings are encouraging and need confirmation in randomized trials.

## 8 | LIMITATIONS

This review has a few limitations. First, we only discuss the impact of *prescription* opioids on the male gonadal axis. We do not review data in men with opioid *addiction* as the two patient populations are quite different. Second, this review is solely dedicated to assessing the effect of opioid analgesics on serum androgens levels and the efficacy of testosterone therapy on various outcomes in men with opioid-induced androgen deficiency. We do not discuss the effects of opioid-induced androgen deficiency on semen quality as the published data are scarce and mainly in men with opioid addiction. The authors intend to prepare another review in which the impact of opioid *addiction* on various endocrine axes, including data on semen quality, will be reviewed.

## 9 | CONCLUSION

Opioid analgesics potently suppress the HPG axis. With continued use of prescription opioids in the United States, the burden of opioid-induced androgen deficiency is likely to be significant. However, there remains a lack of awareness among clinicians regarding the association between opioid use and androgen deficiency, which may translate into lower rate of diagnosis. Clinicians should assess patients on chronic opioid treatment for signs and symptoms of androgen deficiency, such as sexual dysfunction, low bone mass, and reduced quality of life. Androgen deficiency due to opioid use also removes the protection that testosterone provides against nociception, thereby reducing the efficacy of prescribed opioids and leading to increased pain perception. After a careful clinical and biochemical evaluation, symptomatic patients with low testosterone could be started on testosterone therapy as data from randomized trials has demonstrated its efficacy in improving sexual function, body composition, quality of life and nociception. Larger trials of longer duration are needed to confirm

these findings. The ongoing PATH Trial will shed further light on the efficacy and underlying mechanisms of the anti-nociceptive effect of testosterone therapy in men on chronic opioids.

## AUTHOR CONTRIBUTIONS

Study concept and design: All authors. Acquisition of data: All authors. Analysis and interpretation of data: All authors. Drafting of the manuscript: All authors. Funding: None.

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