Secondary adrenal insufficiency and pituitary dysfunction in oral/transdermal opioid users with non-cancer pain

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Abstract

Objective: To evaluate pituitary function, sexual function and quality of life (QoL) in patients on oral or transdermal opioids.

Design and methods: Cross-sectional study comparing pituitary function, QoL and sexual function in people on long-term opioid therapy (n=40) vs an age- and sex-matched control group (n=25). Baseline pituitary function was assessed on blood samples collected prior to 0900 h. Further testing with corticotropin (250 µg IV) and metyrapone (30 mg/kg) stimulation tests was undertaken on participants with serum cortisol <250 nmol/L. Validated questionnaires completed to assess QoL, fatigue and sexual function.

Results: Secondary adrenal insufficiency (SAI) was identified on the basis of a failed stimulation test in 22.5% of opioid users vs no controls (P=0.01). Opioid users with SAI had a higher median morphine-equivalent daily dose (MEDD), P=0.037 – 50% with MEDD >200 mg and 0% with MEDD <60 mg had SAI. Among male participants, testosterone was inversely associated with BMI (P=0.001) but not opioid use. A non-significant trend to low testosterone <8 nmol/L in male opioid users (11/24 opioid users vs 2/14 control, P=0.08) suggests a small subgroup with opioid-induced androgen deficiency. Opioid users had greater fatigue, reduced quality of life in all subsections of the SF-36 and impaired sexual function in both males and females (all scores P<0.001 compared to controls).

Conclusion: Long-term opioid therapy was associated with dose-related SAI in over 20% of chronic pain patients and is associated with poor quality of life, fatigue and sexual dysfunction. Obesity confounds the interpretation of opioid-induced male androgen deficiency.

Introduction

The use of opioid analgesics, particularly oxycodone, for non-cancer pain is increasing in many countries including Australia (1). Adverse effects are common, including drowsiness, gastrointestinal disturbance and an increase in mortality (2). Hormone systems may also be affected. It has been known for several decades that acute administration of opioids intravenously (IV) to humans alters several pituitary hormones (3). This effect is thought to be mediated via inhibition of the relevant hypothalamic releasing factors by opioid receptors which are widely distributed throughout the central nervous system (4, 5, 6).

Less is known about the chronic effects of prolonged oral and transdermal opioid analgesic use on
hypothalamic–pituitary function. With respect to the hypothalamic–pituitary–adrenal (HPA) axis, early studies demonstrated that acute IV morphine and other opioids lowered adrenocorticotropic hormone (ACTH) and cortisol (7). In contrast, high-dose naloxone, an opioid receptor antagonist, results in an increase in ACTH and cortisol (8). This observation led to the notion that ACTH was under the influence of inhibitory central opioid tone, and the extent of central opioid tone could be quantified by the magnitude of the ACTH rise (9). While the use of intrathecal opioids by continuous infusion has been well studied (10), few studies have examined the frequency of clinically significant secondary adrenal insufficiency (SAI) arising from oral or transdermal opioids. We have previously reported a reduced cortisol response to cold pain stimulus, but only 1 out of 10 participants in that study who underwent an ACTH$_{1-24}$ test had a sub-normal result (11). Another recent study undertook ACTH$_{1-24}$ tests on 48 participants on oral opioids and found a sub-normal response in three (12). There are several case reports suggesting rare instances of clinically significant hypocortisolism, including adrenal crisis, induced by opioids (13, 14, 15, 16).

The other commonly affected axis is the hypothalamic–pituitary–gonadal (HPG) axis. Several studies have examined gonadal function in men, concluding that opioids suppress testosterone (17, 18, 19, 20, 21). This is predominantly mediated via suppression of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH), though a partial testicular effect has also been proposed. However, some descriptive studies have lacked a control group, or when a control group was present, the confounding factor of obesity has usually not been considered. Regarding the female HPG axis, previous studies report hypogonadism may occur in women taking long-term opioid analgesia (10, 22). Other pituitary function remains largely unexplored in the context of long-term opioid analgesic use.

The primary aim of this study was to examine the frequency of pituitary dysfunction among people using oral or transdermal opioid analgesics for chronic non-cancer pain compared to an age- and sex-matched control group. The secondary aim was to assess quality of life, fatigue and sexual function in opioid users and controls, examining the relationship between pituitary hormone function and these measures. Our hypothesis was that oral/transdermal opioid analgesics would lead to clinically significant rates of SAI and male androgen deficiency.

Subjects and methods

Participants

People aged 18–75 years either not taking any opioid medications or taking oral or transdermal opioids for >6 months at a dose of ≥25 mg morphine-equivalent daily dose (MEDD) were invited to participate. MEDD was calculated by summing the equivalence of each oral or transdermal opioid taken on an average day. For example, in calculating the MEDD of oxycodone, the most frequently prescribed oral opioid in Australia, the dose is multiplied by 1.5 (40 mg oxycodone=MEDD of 60 mg). Methadone cannot be included in the MEDD calculation due to its uncertain equivalence. Exclusion criteria for both opioid users and controls included active malignancy, active liver or kidney disease, HIV, use of opioids for the treatment of addiction, any form of glucocorticoid treatment such as oral, inhaled, intra-articular or topical within the last month, and in women, exogenous oestrogen use such as the oral contraceptive or menopausal hormone therapy. All participants provided written informed consent and the study was approved by the Ethics Committee of Metro South Health.

Procedure

All participants attended a baseline interview to complete questionnaires and provide details about demographics, medical history and opioid use. Baseline venous blood was drawn between 0700 h and 0900 h in a non-fasting state for quantification of free thyroxine (fT4), thyroid-stimulating hormone (TSH), cortisol, ACTH, DHEAS, prolactin, growth hormone (GH), insulin-like growth factor-1 (IGF-1), follicle stimulating hormone (FSH), LH, testosterone in men and estradiol in women.

Participants whose morning cortisol was <250 nmol/L at the baseline visit were invited to undertake further HPA axis testing with both ACTH$_{1-24}$ test and overnight metyrapone test (OMT). The cut-off of 250 nmol/L is consistent with the recommendations of Auchus et al. (23) in the context of assessing the HPA axis after pituitary surgery and two subsequent studies which demonstrated a very low risk of failing an insulin tolerance test at 6 weeks post operatively (24) or ACTH$_{1-24}$ test at >6 months post operatively (25) when a morning cortisol threshold of 250 nmol/L was applied. The ACTH$_{1-24}$ stimulation test was performed with 250 μg ACTH$_{1-24}$ IV; normal response was defined as 60-min cortisol >500 nmol/L, which has been recently validated locally in a separate study (26).
The OMT involved a single 30 mg/kg dose of metyrapone (maximum 3 g) administered with a glass of milk and a snack between 2300 h and 2400 h and blood sampling for 11-deoxycortisol and cortisol before 0900 h; normal response was defined as 11-deoxycortisol of >200 nmol/L in the presence of cortisol <200 nmol/L. Some participants declined further testing or only presented for the ACTH1–24 test, and one opioid user was commenced on glucocorticoids as part of a treatment protocol for chronic inflammatory demyelinating polyneuropathy prior to any dynamic testing being undertaken. Of the 23 opioid users with a morning cortisol <250 nmol/L, 18 underwent an ACTH1–24 test of whom 15 also underwent an OMT. Of the nine controls with a morning cortisol <250 nmol/L, six underwent ACTH1–24 testing and five the OMT.

Low testosterone in males was defined as a total testosterone of <8 nmol/L, based on the consensus guidelines from the Endocrine Society of Australia in place at the time of study commencement (27). An estradiol of <100 pmol/L plus oligo- or amenorrhoea defined hypogonadism in premenopausal females. Secondary hypogonadism in post-menopausal females was defined as FSH <20 IU/L. Hyperprolactinemia was defined as a prolactin greater than the upper limit of the laboratory sex-specific reference ranges. Thyroid function was compared to the standard laboratory reference intervals for fT4 and TSH. IGF-1 was compared to age-matched reference intervals. The laboratory does not have a well-characterized lower reference interval for DHEAS; this was defined arbitrarily based on the study of Lee et al. of <1 μmol/L in women and <2 μmol/L in men (28). All hormone assays were performed by Pathology Queensland on the standard immunoassay platforms in routine clinical use at the Princess Alexandra Hospital, using the same assay methodology throughout the course of the study.

Quality of life and sexual function questionnaires

Participants completed four validated questionnaires to assess health, wellbeing, fatigue and sexual function. The General Health Questionnaire 28 (GHQ-28) was scored using the bimodal model and overall result was used for analysis (29). The 36-Item Short-Form Health Survey (SF-36) assessed eight components of wellbeing (30). The Chalder Fatigue Score evaluates physical and mental fatigue and was scored using the Likert method (31). Male participants completed the International Index of Erectile Function (IIIEF) to screen for symptoms of hypogonadism including decreased libido and erectile and sexual dysfunction (32). Female participants completed the Female Sexual Function Index (FSFI) questionnaire (33). All questionnaires have been used extensively and previously validated for their intended purpose.

Statistical analysis

Data satisfying parametric assumptions are expressed as mean ± standard error of the mean (s.e.m.) and the two groups (opioid users and controls) were compared using the unpaired t-test. Data which were not normally distributed are expressed as median (interquartile range (IQR)) and the Mann–Whitney U test was used for between group comparisons. The chi-square test was used to assess the differences in categorical variables. Correlations were made using the Pearson or Spearman correlation coefficient depending on whether the data set satisfied parametric assumptions or not respectively. Multiple logistic regression analysis was used to examine the effects of opioid use and BMI on testosterone among the male participants. Data were analysed using GraphPad Prism version 7 and SPSS version 24.

Results

Demographics

Forty people (25 male and 15 female) aged 18–75 years prescribed oral or transdermal opioid analgesics for chronic pain for a duration of >6 months at a dose of ≥25 mg morphine-equivalent daily dose (MEDD) were recruited along with 25 control participants (14 male and 11 female) not taking opioids. The controls were matched for age and sex (Table 1). Most participants (90%) in the opioid user arm were recruited from the Metro South Health Persistent Pain Clinic, and the remainder from other hospital clinics. The most common indications for opioid therapy were musculoskeletal pain (27), neuropathic pain (6) and chronic abdominal pain (5). Twenty-four of the 25 controls were recruited from the community, including some hospital staff. Of these, two reported chronic pain managed with infrequent non-opioid analgesia. One control participant was a patient of the Persistent Pain Clinic, not managed on opioids. One male participant in the opioid user arm had received exogenous testosterone – his data were excluded from the analyses of the HPG axis but included for other parameters. Opioid users reported a mean morphine-equivalent daily dose (MEDD) of 74 mg (range 25–265 mg) at the time of study for a mean duration of 4 years (range: 1–25 years).
Table 1  Demographics of study participants. Data are expressed as mean (range).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Opioid users</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (M:F)</td>
<td>25:15</td>
<td>14:11</td>
<td>0.51</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 (22–72)</td>
<td>49 (25–65)</td>
<td>0.35</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29.7 (17.5–66.7)</td>
<td>25.6 (18.5–38.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Smoking status (current/former/never)</td>
<td>17/7/16</td>
<td>2/5/18</td>
<td>0.006</td>
</tr>
<tr>
<td>Alcohol intake (grams per week)</td>
<td>0 (0–300)</td>
<td>20 (0–280)</td>
<td>0.042</td>
</tr>
<tr>
<td>Morphine-equivalent daily dose (mg)</td>
<td>74 (25–265)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Duration of opioid use (years)</td>
<td>4 (1–25)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Nineteen of the 40 opioid users were taking one opioid, 17 were taking two and 4 were taking 3 different opioids, with oxycodone being the most frequently used. Two patients taking methadone did not have this formulation included in the MEDD calculation. Opioid users had a higher median (IQR) BMI 29.7 (25.1–36.9) kg/m² vs controls 25.6 (20.6–31.2) kg/m², P=0.011) and were more likely to be a current smoker (P=0.006).

Baseline pituitary function

Hormone results are presented in Table 2. Participants on long-term opioid therapy had lower levels of free T4 (P=0.002), DHEAS (P=0.008) and IGF-1 (P=0.004). Other baseline morning hormone concentrations relating to thyroid, adrenal and gonadal axes and prolactin were not significantly different between groups. While mean values for morning cortisol were not significantly lower in opioid users, 20% of opioid users had sub-normal cortisol values <18.0 nmol/L (13–21) vs 11.1 nmol/L (5.6–23) of the control participants (0%, P=0.95). DHEAS concentration nor rate of sub-normal results was correlated to cortisol levels or abnormal HPA axis stimulation testing.

Hypothalamic–pituitary–gonadal axis stimulation testing

Nine of the opioid users (22.5%) failed either the ACTH1-24 test (N=6) or OMT (N=3), compared to none of the control participants (0%, P=0.01). All nine of these participants underwent the ACTH1-24. Of the six participants who failed the ACTH1-24 test, two passed and three failed the OMT and one did not complete the test. The morning cortisol in the participants who failed a stimulation test ranged from 29 to 203 nmol/L, with 8/9 being <200 nmol/L. Opioid users who failed a stimulation test had a significantly higher median MEDD of 100 mg, compared to 60 mg in the remaining subjects (Fig. 1, P=0.037). None of the opioid users with MEDD below 60 mg had abnormal stimulation testing, while 4/8 (50%) of those whose MEDD was >200 mg had SAI. No participants were commenced on glucocorticoids by the investigators.

Hypothalamic–pituitary–gonadal axis

There was no evidence of FSH and LH suppression among the female opioid users of post-menopausal age, while there were insufficient numbers of premenopausal women (n=5 opioid users) to evaluate the effect of opioids on menstrual cyclicity.

For male participants, serum testosterone was not significantly different between opioid users and controls, either for mean testosterone (9.2±0.9 nmol/L opioid vs 11.1±0.9 nmol/L control, P=0.19) or rates of sub-normal testosterone <8 nmol/L (11/24 (46%) opioid vs 22/51 (43%) control, P=0.79). There was no evidence of gonadal function suppression among the female opioid users of post-menopausal age, while there were insufficient numbers of premenopausal women (n=5 opioid users) to evaluate the effect of opioids on menstrual cyclicity.

Table 2  Baseline pituitary function testing. Data are expressed as mean±s.e.m. with normal distribution or median (IQR).

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Opioid users</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free T4 (pmol/L)</td>
<td>9.7±0.2</td>
<td>10.7±0.3</td>
<td>0.002</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.7±0.15</td>
<td>1.6±0.17</td>
<td>0.46</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>236±17</td>
<td>280±18</td>
<td>0.10</td>
</tr>
<tr>
<td>ACTH (ng/L)</td>
<td>12 (10–22)</td>
<td>15 (10–20)</td>
<td>0.60</td>
</tr>
<tr>
<td>DHEAS (µmol/L)</td>
<td>2.0 (1.1–3.0)</td>
<td>3.0 (2.1–4.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Testosterone M (nmol/L)</td>
<td>9.2±0.9</td>
<td>11.1±0.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Testosterone F (nmol/L)</td>
<td>0.9±0.2</td>
<td>1.0±0.15</td>
<td>0.84</td>
</tr>
<tr>
<td>FSH M (IU/L)</td>
<td>5.8±0.5</td>
<td>4.4±0.4</td>
<td>0.08</td>
</tr>
<tr>
<td>FSH F (IU/L)</td>
<td>28 (4.5–79)</td>
<td>15 (5.2–61)</td>
<td>0.72</td>
</tr>
<tr>
<td>LH M (IU/L)</td>
<td>3.6±0.4</td>
<td>3.7±0.3</td>
<td>0.80</td>
</tr>
<tr>
<td>LH F (IU/L)</td>
<td>20 (5.3–35)</td>
<td>11 (5.6–23)</td>
<td>0.67</td>
</tr>
<tr>
<td>E2 M (pmol/L)</td>
<td>89.7±8.7</td>
<td>86.4±6.8</td>
<td>0.79</td>
</tr>
<tr>
<td>E2 F (pmol/L)</td>
<td>264.9±76.9</td>
<td>220.7±42.5</td>
<td>0.64</td>
</tr>
<tr>
<td>Prolactin (mU/L)</td>
<td>177 (125–304)</td>
<td>169 (146–241)</td>
<td>0.95</td>
</tr>
<tr>
<td>IGF-1 (nmol/L)</td>
<td>18.0 (13–21)</td>
<td>22.0 (18–28)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

f, female; M, male.
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2/14 (14%) control, \( P = 0.08 \). Serum testosterone was negatively correlated with BMI across all participants (Fig. 2A, \( R = -0.50, P = 0.001 \)). Multiple regression analysis performed to control for BMI found a significant independent effect of BMI: \( \beta = -0.481, P = 0.002 \), but not opioid use: \( \beta = 0.155, P = 0.29 \). However, there did appear to be a small number of men on opioids whose testosterone was lower than expected for BMI (Fig. 2A, encircled group).

There was no association between SAI and male androgen deficiency. Of the four men who failed the ACTH\(_{1-24}\) test or OMT, only one had a serum testosterone <8 nmol/L.

Quality of life and sexual function

Opioid users had worse scores on all questionnaires (Table 3). In the SF-36, compared to controls, opioid users reported impaired physical, social and emotional role functioning, bodily pain, mental health, vitality and general health. All domains reached significance with \( P < 0.001 \).

Sexual function was markedly impaired both in male and female opioid users compared to controls. Mean IIEF scores were 27.6 for opioid users and 65.5 for controls (\( P < 0.001 \)), while mean FSFI scores were 11.7 for opioid users and 25.9 for controls (\( P < 0.001 \)). Lower scores on the IIEF were not associated with serum testosterone (Fig. 2B, \( P = 0.45 \)).

Among the opioid users, there was a positive association between bodily pain score of the SF-36 and morning cortisol, such that low cortisol was associated with increased bodily pain (Fig. 3, \( R = 0.47, P = 0.003 \)). The GHQ-28 also showed significantly lower QoL in opioid users compared to controls (score of 12 among opioid users vs 0 in controls, \( P < 0.001 \)). Opioid users exhibited higher Fatigue Scale scores compared to controls (19.8 vs 10.9, \( P < 0.0001 \)), with no relationship to morning cortisol (\( P = 0.94 \)) or failure of stimulation testing (\( P = 0.64 \)).

![Figure 1](https://eje.bioscientifica.com)

Comparison of the morphine-equivalent daily dose (MEDD) of opioid users with intact HPA axis (□) vs those who failed one or both of the ACTH\(_{1-24}\) test or the OMT (▲). *\( P = 0.037 \) Mann–Whitney U test.

![Figure 2](https://eje.bioscientifica.com)

(A) Relationship between morning serum testosterone and BMI, combining male opioid users (○) and controls (■). \( R = -0.50, P = 0.001 \). 11/25 male opioid users vs 2/11 controls had a serum testosterone <8 nmol/L, \( P = 0.08 \). Circle indicates the six opioid users with testosterone <8 nmol/L and BMI <30 kg/m\(^2\). (B) Relationship between morning serum testosterone and IIEF score (male sexual function). There was no correlation between serum testosterone and IIEF score, \( R = 0.29, P = 0.09 \). Male opioid users had significantly lower IIEF score than controls.
**Discussion**

This study demonstrates significant rates of secondary adrenal insufficiency in patients with long-term oral or transdermal opioid use. Adrenal insufficiency based on ACTH$_{1-24}$ and/or metyrapone stimulation testing was found in 22.5% of opioid patients, compared to none of the control patients. Additionally, opioid users were more likely to have morning serum cortisol level below 5 µg/dL (138 nmol/L) predictive of adrenal insufficiency (34).

Patients who failed a stimulation test had higher median morphine-equivalent dose. Furthermore, no patient whose MEDD was < 60 mg had adrenal insufficiency, while the rate in those with MEDD > 200 mg was 50%. These findings support the hypothesis that patients taking long-term opioid analgesia are at risk of opioid dose-related HPA axis suppression.

While these data demonstrate biochemical adrenal insufficiency, the clinical significance with respect to the need for glucocorticoid replacement is unclear. None of the opioid users had a history of medical events consistent with adrenal crises. While isolated cases of adrenal crisis attributed to opioid use have been reported, these are very limited in comparison to the large numbers of opioid users throughout the world. Additionally, the heterogeneity of cortisol means some individuals have higher cortisol on opioids, which could be related to effects of depression, stress or illness. While QoL questionnaire responses were universally poorer among opioid users, with the exception of the bodily pain section of the SF-36, these did not predict biochemical SAI. This study found no association between SAI and fatigue, as opioid users universally reported symptoms of fatigue.

Opioid users with lower cortisol levels reported worse bodily pain. One explanation for this finding is that chronic stress responses to pain may cause a stress-induced hypocortisolism, suggesting that the pain itself is causing the HPA dysfunction (35). The converse of this relationship may also be true, as cortisol is a potent anti-inflammatory and SAI may cause worsening of inflammation contributing to pain. Nenke et al. conducted a pilot randomized placebo-controlled trial of physiological cortisol replacement in patients taking opioids for chronic non-cancer pain demonstrating that physiological glucocorticoid replacement improved pain tolerance (11). This improvement suggests a component of symptoms such as pain intolerance may be attributed to hypocortisolism. Further studies of the benefits of glucocorticoid replacement are required to clarify whether opioid users with biochemical cortisol deficiency demonstrate improvement of key symptoms.
The morning cortisol threshold of 250 nmol/L was chosen to minimize an unnecessary burden of testing in people with a low probability of having an abnormal HPA axis; the cited literature (23, 24, 25) shows approximately a 95% probability of passing the ACTH_{1-24} test above this level. We acknowledge that one or two cases of adrenal insufficiency may have been missed using this approach. We used standard HPA axis stimulation tests in routine clinical use in our department, which have been recently compared with the ITT and validated in the setting of pituitary surgery (36). While the insulin tolerance test is considered the gold standard, this would not be the test that the average practising clinician would order for a patient on opioids, and we wanted the study to have clinical relevance. The rationale behind doing both the ACTH_{1-24} test and OMT was primarily as a ‘double check’ for participants who fit the well-described scenario of passing the ACTH_{1-24} test but having SAI (37). While not all participants with a morning cortisol <250 nmol/L completed the dynamic testing protocol, the proportions undertaking dynamic tests did not differ between opioid users and controls.

This study is the first to use a control arm to compare rates of SAI in users of oral or transdermal opioids, and the first to concurrently evaluate sexual function and quality of life. Our findings are however broadly consistent with similar studies. The identified rate of 22.5% of patients with SAI is somewhat higher than that in the study by Gibb et al. who screened a cohort of patients receiving opioids for chronic non-cancer pain with ACTH_{1-24} stimulation testing. They reported low morning cortisol <100 nmol/L in 8.3% and 3/48 failing an ACTH_{1-24} test (12). Of note however, was that all three of the patients in this study identified with adrenal insufficiency had a MEDD ≥60 mg. Even if the participants who passed the ACTH_{1-24} test but failed the OMT are disregarded, the rate of SAI based only on the ACTH_{1-24} test is 15% – considerably higher than the Gibb et al.’s study which was 8.3%. A study on 66 patients taking opioids for chronic non-malignant pain found that opioid treated patients had sub-normal DHEAS levels in 67% of opioid users compared to 8% of controls, but maintained normal ACTH (38). The presence of normal ACTH levels with sub-normal DHEAS may indicate failure of feedback mechanisms to cause central stimulation of ACTH, decreased DHEAS production at the adrenal gland due to inhibition of 17,20-lyase activity and/or inhibition of 3 beta-hydroxysteroid dehydrogenase enzymes as described in critical illness (39) or a combination of the two. This provides context and a suggested mechanism for the finding of lower DHEAS in this study. Other evidence for chronic effects of opioid administration on the HPA axis is a series of case studies describing patients on long-term opioids found to have SAI, which resolved with opioid cessation and, if rechallenged, relapsed following recommencement of opioid therapy (13, 14, 15, 16).

HPG axis suppression was anticipated among male opioid users. Morning serum testosterone showed sub-normal values in 46% of male opioid users compared to 14% of control participants, but this failed to reach statistical significance. We found no gonadotropin suppression among the post-menopausal female opioid users, while there were insufficient numbers of premenopausal women to evaluate the effect of opioids on menstrual cyclicity.

There was a significant inverse relationship between serum testosterone and BMI among male opioid users and controls, consistent with the known effects of obesity. Opioid users reported more symptoms of sexual and erectile dysfunction in IIEF responses, but poorer scores did not correlate with serum testosterone. In contrast, several other studies on patients treated with opioids have found evidence of ‘opioid-induced androgen deficiency’, reported to occur at a rate of 64–100% which is significantly higher than non-opioid-treated patients with chronic pain in studies that were controlled (17, 18, 19, 20, 21). Some of these studies note low-normal LH and FSH in patients with low testosterone suggesting hypothalamic–pituitary suppression as the mechanism for reduced testosterone (17, 18, 19, 21). The consistency of this finding between studies and across treatments indicates an association between opioid use and androgen deficiency. However, our study highlights the role of an elevated BMI as an important consideration in the interpretation of testosterone results among opioid users. Of the other studies, only Daniell et al. discussed the possible influence of higher BMI in the opioid group, but this was not controlled for during statistical analysis. We suggest that rates of opioid-induced male hypogonadism of up to 100% in the literature are likely to be an overestimate, confounded by obesity, but acknowledge that our data are limited by small numbers. Six out of 24 male opioid users had a serum testosterone <8 nmol/L and a BMI <30 kg/m^2, suggesting a subgroup of male opioid users likely to have genuine opioid-induced androgen deficiency. Interestingly, there was dissociation between the presence of testosterone deficiency and adrenal insufficiency among the male patients. This may be due to different opioid receptors being implicated in the regulation of GnRH vs CRH (4).
The presence of sexual dysfunction across the male opioid cohort regardless of biochemical hypogonadism raises the question of whether sexual function can be improved with testosterone replacement. Recent pilot randomized-controlled trials have shown that testosterone replacement not only improves sexual function in opioid users, but also improves pain sensitivity, resulting in lower required opioid dose (40, 41). Our data suggest however, that individuals suffering from biochemical hypogonadism are difficult to distinguish based on symptomatic sexual dysfunction. Information required to identify the best management strategies includes determining which individuals benefit from treatment and whether other potential means of increasing testosterone are effective in these patients such as opioid dose reduction, rotation of opioid formulation or the use of alternative therapy such as clomiphene citrate (42).

Regarding other aspects of pituitary function, free thyroxine and IGF-1 concentrations were found to be lower in opioid users than in controls. This study is the first in humans to examine these aspects of pituitary function in long-term oral or transdermal opioid analgesic use. Studies examining thyroid and GH axes in intrathecal opioid use or heroin addiction show varying results (6, 10). Given the small difference in mean values and the fact that none of the opioid users had levels below the lower limit of the reference ranges, it is unclear whether these findings have any clinical significance.

Strengths of this study design include the use of controls for age and sex, and the use of validated questionnaires in conjunction with hormone evaluation. However, this study model cannot isolate the effect of chronic opioid use alone. Opioid users are a heterogeneous group, often with different indications for analgesia and multiple co-morbidities including importantly the presence of chronic pain itself, which may affect the HPA and HPG axes. Participant numbers are modest; recruitment to the study was challenging. While recruitment by invitation may result in selection bias including reduced QoL as motivation to participate, inhaled glucocorticoid use was a common reason for ineligibility, as was unwillingness to get to the clinical research centre before 0900h. The cross-sectional design used in this study investigates the effect of opioids in a way that is reflective of current practice in a real-world setting, as recruiting an opioid-free control arm of people with similar levels of pain and co-morbidities is impractical due to the widespread use of opioid medications in this population. Ideally a prospective randomised controlled trial administering opioids vs non-opioid analgesics to chronic pain sufferers would be most effective at isolating the endocrine effects of opioid use.

In summary, dose-related secondary adrenal insufficiency in more than 20% of patients on long-term oral and transdermal opioids is a novel observation. While the therapeutic implications of a failed stimulation test remain unclear in this population, people on a MEDD of <60mg appear to be at low risk of developing secondary adrenal insufficiency. Obesity confounds the interpretation of opioid-induced male androgen deficiency. Opioid use is associated with poor quality of life, reduced sexual function and multiple co-morbidities, making interpretation of the relationship between hormonal tests and symptoms challenging. Further refinement is required to identify those men who will benefit from testosterone replacement. There is also a need for more systematic evaluation of the HPA axis in opioid users and additional, longer term controlled trials of physiological glucocorticoid substitution in those failing a stimulation test. Other management options for hormone insufficiency states include opioid dose reduction or cessation. The endocrine complications of opioid use need to be considered, along with the many other dangers of opioids in patient care.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement
A L recruited participants, undertook the blood sampling, supervised the QoL questionnaire administration, undertook the initial statistical analysis and wrote the first draft of the manuscript. J S assisted with blood sampling, HPA axis testing and questionnaire administration. C J assisted with participant recruitment, data analysis and was co-supervisor of A L’s Master of Philosophy degree. D J T assisted with study design, data analysis and interpretation. W J L primarily designed the study, assisted with participant recruitment, data analysis and interpretation and was principal supervisor of AL’s Master of Philosophy degree. All authors were involved in revision and approval of the final manuscript.

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References


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