

Opioids and their endocrine effects

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1 **Opioids and their endocrine effects:**

2 **A systematic review and meta-analysis.**

3

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30 **Abstract**

31 CONTEXT: The increased use of opioids has resulted in an unprecedented opioid epidemic. Chronic
32 opioid use causes hypogonadism, but its frequency, as well as the effects of opioids on other
33 hypothalamo-pituitary-end organ hormone axes, remains unclear.

34 OBJECTIVE: The aim of this systematic review and meta-analysis was to assess the effects of opioid
35 use on pituitary function.

36 METHODS: Eight electronic databases were searched for articles published up to May 8, 2018. Fixed-
37 or random-effects meta-analysis was performed to estimate pooled proportions with 95%
38 confidence intervals. This study is reported following the PRISMA- and MOOSE-guidelines.

39 DATA SYNTHESIS: 52 studies (22 low risk of bias) were included describing 18,428 subjects,
40 consisting of patients with chronic pain (n=21 studies), or on maintenance treatment for opioid
41 addiction (n=9) and healthy volunteers (n=4). The most frequently used opioid was methadone
42 (n=13 studies), followed by morphine (n=12). Prevalence of hypogonadism was 63% (95% CI: 55-
43 70%, 15 studies, 3,250 patients, 99.5% males). Prevalence of hypocortisolism relying on dynamic and
44 non-dynamic testing was 15% (95% CI: 6-28%, 5 studies, 205 patients, 57.5% males) and including
45 only studies using the insulin tolerance tests 24% (95% CI 16-33%, 2 studies, n=97 patients). In 5 out
46 of 7 studies hyperprolactinemia was present. No clear effects on the somatotropic and
47 hypothalamo-pituitary-thyroid axes were described.

48 CONCLUSIONS: Hypogonadism occurs in more than half of male opioid users, and hypocortisolism in
49 approximately a fifth of all patients. Periodical evaluation of at least the gonadal and adrenal axes is
50 therefore advisable.

51 **Précis**

52 In this systematic review and meta-analysis, we found that hypogonadism occurs in more than half
53 of male opioid users, and hypocortisolism in approximately a fifth of all patients.

54

55 **Introduction**

56 Over the past two decades, the use of opioids and the number of opioid-overdose related deaths
57 has steadily increased [1]. In the United States alone, there were more than 11 million people with
58 misused prescription opioids and 42,000 opioid-related deaths were reported in 2016 [2-4]. Long-
59 term opioid use is associated with adverse effects, the most common being constipation, nausea,
60 and dyspepsia [5, 6]. In addition, several studies suggest that the endocrine system is affected in
61 opioid users. [7, 8].

62 In addition, many animal studies have been performed on the mechanisms of opioid-induced
63 endocrine effects. It has been shown that opioids inhibit the gonadal axis in the hypothalamus via ϵ -
64 receptors and stimulate prolactin secretion via μ -, κ - and δ -receptors. Thus, GnRH-release and the
65 gonadal axis may be additionally suppressed by opioid-induced hyperprolactinemia [2]. Lastly,
66 opioids induce the conversion of testosterone to dihydrotestosterone [9]. The corticotrophic axis may
67 be modulated via effects on the κ - and δ -receptors in the hypothalamus and pituitary gland and the
68 somatotroph axis via μ -, κ - and δ -receptors in the hypothalamus [2].

69 Although hypogonadism, and to a lesser extent hypocortisolism, are recognized endocrine side
70 effects, their prevalence remains unclear [10, 11]. Dysfunction of both axes may result in significant,
71 often incapacitating symptoms [2]. Both male and female patients with hypogonadism may suffer
72 from sexual dysfunction and decreased libido. Male patients can present with erectile dysfunction,
73 impotence, and gynecomastia, while female patients can have menstrual irregularities. In addition,
74 hypocortisolism can manifest a wide variety of symptoms, such as fatigue, malaise, abdominal
75 discomfort, anorexia, and orthostatic hypotension. Possible effects of opioids on the secretion of
76 growth hormone (GH), thyroid-stimulating hormone (TSH), and prolactin, remain unelucidated and
77 have not been systematically reviewed [2, 12-17].

78 Due to the increased use of opioids, it has become increasingly important to identify the prevalence
79 and impact of opioid exposure-related endocrine deficits. Our goal was, therefore, to assess the
80 reported effects of opioids on the endocrine system through a systematic review and meta-analysis.

81 **Materials and methods**

82 This systematic review and meta-analysis was reported according to the Preferred Reporting Items
83 for Systematic Reviews and Meta-Analysis (PRISMA) statement [18] and the Meta-analyses Of
84 Observational Studies in Epidemiology (MOOSE) guideline [19] for randomized and observational
85 studies, respectively. Screening of studies, data extraction, and risk of bias assessment were
86 performed by two independent reviewers (FdV, MB). Disagreement was solved through discussion.
87 If discussion failed to lead to a consensus, a third reviewer was consulted (AHZN) to reach
88 consensus.

89 **Search strategy**

90 A literature search was conducted to identify studies describing endocrine effects of opioid use. The
91 following databases were systematically searched for relevant studies with help of an experienced
92 librarian (JWS): PubMed, Embase, Web of Science, COCHRANE Library, Emcare, Academic Search
93 Premier and ScienceDirect up to May 8, 2018 and processed to an EndNote X9 database (Clarivate
94 Analytics, Philadelphia, PA, US). Terms or derivatives of these terms included in the search strategy
95 were “opioids”, “hypogonadism”, “adrenal insufficiency”, “growth hormone deficiency”,
96 “hypothyroidism” and “prolactin”. Furthermore, terms formulated to exclude animal studies were
97 used. The reference lists of included studies were reviewed to identify additional relevant studies.
98 The complete search strategy is presented in the supplemental document 1.

99 **Eligibility criteria and article selection**

100 Randomized controlled trials, longitudinal, and cross-sectional cohort studies assessing the
101 endocrine status in patients using opioids were eligible for inclusion. Studies were excluded, if the

102 study population (partially) consisted of children (aged < 18 years), or if studies were not in English.
103 Additionally, studies not reporting original data (e.g. reviews), case reports, and unpublished studies
104 (e.g. congress abstracts) were excluded from analysis. Studies were screened by title and abstract
105 and potentially relevant studies were reviewed by full-text analysis.

106 **Data extraction**

107 The following data was extracted, if available: main inclusion and exclusion criteria, number of
108 included subjects, age, percentage of male subjects, opioid type, duration of opioid exposure,
109 duration of follow-up, endocrine axis (including evaluation method), and the effects of opioid
110 exposure on the described axes. Where possible, the number of patients with endocrine
111 dysfunction(s) were extracted. Finally, results of hormone replacement therapies in case of
112 presumed endocrine deficiencies were extracted when available. Twenty authors of studies
113 reporting on the function of the hypothalamo-pituitary-gonadal, and hypothalamus-pituitary-
114 adrenal (HPA) axis were contacted and asked to provide additional data on the prevalence of these
115 respective deficiencies. In case of no response, authors were approached a second time, however,
116 ultimately no additional (subject level) data could be obtained.

117 **Risk of bias assessment**

118 The following risk of bias components were assessed among all studies:

- 119 1. Consecutive inclusion of patients
- 120 2. Adequate endocrine testing
- 121 3. Risk of confounding of effects of opioids on the endocrine system among comparative
122 studies (e.g. comparison of opioid addicts and healthy controls, correction with multivariate
123 analyses)

124 Studies were assigned to qualitative categories for each element of the risk of bias analysis and were
125 defined as low, moderate, or high risk for each element separately (the scoring system is presented

126 in the supplemental document 2). Adequate endocrine testing was considered the most important
127 element of the final risk of bias classification. Studies with a low risk of bias on the endocrine
128 assessment and at least one of the other two criteria were assigned a low risk of bias. Potential
129 differences between studies were used to assess the between-study heterogeneity. This was largest
130 in endocrine assessment of the HPA-axis and, therefore, we performed a separate assessment based
131 on studies using the insulin tolerance test (ITT).

132 **Study endpoints**

133 The primary outcome measure was the percentage of patients with dysfunction of one or more
134 pituitary axes (see supplementary tables S1-S6 for the reported definitions of endocrine
135 dysfunctions). Furthermore, we systematically reviewed the effects of opioids on the various
136 hypothalamic-pituitary-end organ axes [gonadal, adrenal, thyroid, somatotroph, and prolactin
137 secretion], as well as the effects of hormone replacement on opioid-related endocrine deficiencies.

138 **Statistical analysis**

139 A random-effects logistic regression model was performed when there were 5 or more studies per
140 analysis to estimate pooled percentages. A fixed-effects model was used for analyses with fewer
141 than 5 studies. In order to prevent exclusion of studies with a 0% or 100% outcome, the Freeman-
142 Tukey arcsine transformation was used to stabilize variances. For outcomes that included 5 or more
143 studies per analysis, the I^2 statistics were used for the quantification of between-study
144 heterogeneity. For analysis with less than 5 studies, no quantification of between-study
145 heterogeneity was estimated due to reliability issues [20]. All analyses were performed using Stata
146 14 (Stata Corp., College Station, TX, USA). Sensitivity analysis for the gonadal axes was performed by
147 analyses of studies with a low risk of bias. For the meta-analysis of studies that analyzed the HPA-
148 axis, sensitivity analysis was performed including only studies that used the ITT as assessment
149 method.

150 **Results**

151 **Study selection**

152 The literature search yielded 1,123 unique articles. After the exclusion of studies based on title and
153 abstract, we screened 118 full-text articles. Ultimately, 52 studies were included (Fig 1,
154 supplemental document 3). Of all studies, 22 were classified with a low risk of bias, 10 with a
155 moderate, and 20 with a high risk of bias. The full risk of bias assessment is presented in
156 supplementary table S7.

157 **Study characteristics**

158 Of the 52 included studies, 34 analyzed the effect of opioids on the gonadotropic axis, 24 on the
159 HPA-axis, 8 on the hypothalamo-pituitary-thyroid (HPT) axis, 9 on prolactin secretion, and 5 on the
160 somatotrophic axis. In addition, 6 studies reported on the effect of testosterone replacement in case
161 of associated hypogonadism, one on the effect of treatment with hydrocortisone on
162 hypocortisolism, but there were no studies reporting on the effects of hormone replacement on
163 other axes. Studies were published between 1970 and 2018, but 32 (62%) were published after
164 2010. Methadone was the most frequently reported opioid (n=13), followed by morphine (n=12).
165 Eight studies defined the opioid dose as the morphine equivalent daily dose (MEDD). Most studies
166 were performed in the United States (n=18), Europe (n=18), or Australia (n=6).

167 **Results**

168 **Meta-analysis of HPA-axis and gonadal axis deficiency**

169 **Fifteen** studies that included a total of 3,250 patients presented data on the percentage of patients
170 with hypogonadism among chronic opioid users, based on a single (morning or random)
171 testosterone measurement (Table 1). **99.5% percent of the analyzed patients were males (n=3,234).**
172 The percentage of patients with hypogonadism ranged between 36 and 100%, with a weighted

173 mean percentage of 63% (95% CI: 55-70%). Sensitivity analysis, among 7 studies with a low risk of
174 bias, showed hypogonadism among 69% of **male** patients (95% CI: 50-85%) (Fig. 2).

175 Five studies presented data of 205 patients (58% male) with hypocortisolism (Table 1). The
176 percentage of patients with hypocortisolism ranged from 5% to 42%, with a weighted mean
177 percentage of 15% (95% CI: 6-28%). Sensitivity analysis, including 2 studies performing an ITT,
178 showed that 24% of patients (95% CI: 16-33%) were classified as adrenal insufficient (Fig. 3).

179 **Systematic review of all hypothalamus-pituitary-end organ axes**

180 **Hypothalamo-pituitary-gonadal axis** (Supplementary Table S1)

181 All 27 studies (n=16,256 patients) reported an inhibitory effect of opioids on the hypothalamic-
182 pituitary-gonadal axis. **The effects on the gonadal axis of each gender are reported separately.**

183 **Male hypothalamo-pituitary-gonadal axis**

184 Most studies specifically evaluated gonadal function only in male patients on opioids (n=15). Male
185 patients on fentanyl, methadone, or oxycodone had increased odds for testosterone deficiency
186 compared to those using hydrocodone [odds ratios (OR) 25.73, 7.33, and 3.15] [10]. When
187 comparing long-acting with short-acting opioids, patients on long-acting ones had higher odds (OR
188 3.39, 95% CI 2.39-4.77) for testosterone deficiency [10]. Another study showed hypogonadism
189 among 57% (n=351) of patients on long-acting opioids and among 35% (n=340) of patients on short-
190 acting opioids [21]. Two studies reported on a dose-related pattern [21, 22]. The odds for androgen
191 deficiency were higher on high dose methadone (OR 1.16) than low dose (OR 1.01) as compared to
192 controls [21]. Moreover, total testosterone levels were lower in high dose (172.1ng/dL),
193 intermediate dose (188.5) and low dose users (265.8) as compared to controls (449.1) [22].
194 Regarding symptomatology, the results were limited. One study found no correlation between
195 sexual dysfunction and opioid use [23], while others reported increased rates of male patients with
196 reduced potency [24], lower sexual desire [25], erectile dysfunction [26] or with general sexual

197 dysfunction [16] whilst on opioids. Specifically, impotence and erectile dysfunction were reported in
198 89% of opioid using male patients (n=48) [22]. Importantly, 23 of 24 males (95.8%) recorded a rather
199 sudden decrease and even disappearance of libido and potency shortly after initiating opioid
200 administration in one study [7]. Lastly, 50% of patients on morphine had osteopenia (T-score
201 between -1.0 and -2.5 SD), and 21.4% had osteoporosis (T-score at or below -2.5 SD) [27].

202 Female hypothalamo-pituitary-gonadal axis

203 Studies reporting specifically on the female HPG-axis are very limited (n=2). Two studies found an
204 inhibitory effect on serum total and free testosterone concentrations in women, while serum
205 oestradiol was not affected [23, 28]. In one study, decreased libido and hot flashes were more
206 frequent in women receiving morphine [24], while libido decreased or disappeared shortly after
207 initiating opioid therapy in 67% (n=22) in another [7]. Amenorrhea was reported in 19% (n=3) [24]
208 and 67% (n=14) [7] and irregular menses in 50% (n=8) [24] and 33% (n=7) [7] of opioid using
209 premenopausal women in two studies, while menstrual cycle disorders were present in 87% of
210 premenopausal women on long-term opioids [16]. Another study reported that lower androgen
211 levels were correlated to depressive symptoms in women on intrathecal opioids [26].

212 **Hypothalamic-Pituitary-Adrenal axis** (Supplementary Table S2)

213 In total, 21 studies with 1,095 patients described the effects of opioid use on the activity of the HPA-
214 axis. Of these, 9 reported an inhibitory effect, 4 a stimulatory effect, and 8 studies reported no effect
215 [12-14, 29-32]. Evaluation of the HPA-axis was performed in most studies by measurement of non-
216 stimulated salivary, or serum cortisol (n=12). A stimulation test was used in 8 of the studies (n=208)
217 of which 2 used the insulin tolerance test (ITT), 2 the adrenocorticotrophic hormone (ACTH)
218 stimulation test, 1 the corticotropin-releasing hormone (CRH) stimulation test, 1 the metyrapone
219 test, and 1 yohimbine-stimulated cortisol. The two largest studies (n=176 and n=170), showed lower
220 blood cortisol and ACTH levels in opioid users as compared to controls [12, 14]. A dose-response
221 relationship between opioid use and cortisol levels was reported by two studies, with a lower fasting

222 cortisol (decrease of 8.6nmol/L for every 10mg morphine equivalent) [12] and a higher incidence of
223 inadequate cortisol response to ACTH stimulation with higher dosages of opioids (0% on low-dose vs
224 9% (n=3) on high-dose) [13]. The two studies using ITT reported inadequate cortisol peaks 22% (n=4)
225 of the control subjects compared to 33% (n=6) of the patients on intrathecal opioids and in 50%
226 (n=9) of those on oral opioids [24], and that 15% of the opioid users had an insufficient cortisol
227 response [7].

228 **Clinical data on HPA-axis morbidity in opioid users is very limited to absent. Abs *et al.* did report a**
229 **patient with HPA-axis insufficiency that developed symptomatology of an Addisonian crisis during an**
230 **episode of fever due by pneumonia. The patient recovered with supplementation of corticosteroids**
231 **[7].**

232 One study using a health status questionnaire showed that chronic pain patients with opioid-
233 induced hypocortisolism offered low-dose hydrocortisone replacement reported better scores on
234 vitality and pain compared with the placebo group [33].

235 **Hypothalamic-Pituitary-Thyroid (HPT) axis** (Supplementary Table S3)

236 Seven studies, including 274 patients, described the results of the effects of opioids on the HPT-axis.
237 One study showed that higher TSH-levels were seen after acute administration of morphine
238 compared to those prior to administration [15]. Additionally, higher TSH levels following thyrotropin-
239 releasing hormone (TRH) stimulation were found among patients on long-term opioids compared to
240 healthy controls [16]. One study found lower serum fT4 values amongst high-dose kratom (opioid
241 tea) (>3 glasses daily) users compared to low-dose users (≤3 glasses daily) (14.3 vs 16.2mU/L) [34].
242 Another study found lower serum fT4 in 6 out of 19 (32%) patients on intrathecal opioids and in 6
243 out of 18 (33%) patients on oral opioids, compared to 0 (0%) healthy controls [24].

244 **Prolactin secretion** (Supplementary Table S4)

245 Seven studies (n=354 patients), reported results on the effects of opioids on prolactin secretion.
246 Four studies showed an increase in serum prolactin levels among patients on opioid analgesics [7,
247 16, 23, 29], whereas another study reported that 40% of patients (n=8) had hyperprolactinemia, and
248 all other patients had normal prolactin levels [8].

249 **Somatotropic axis** (Supplementary Table S5)

250 Five studies described the effect of opioids on the somatotropic axis amongst 234 patients. One
251 study showed lower serum insulin-like growth factor 1 (IGF-1) among 71 intrathecal opioid users
252 compared to 20 controls (138.5 vs 162.0 μ g/L) and a lower GH peak during an ITT (14.5 vs 20.9 μ g/L)
253 [7]. In another study, a low ITT GH-peak (<3.2ng/mL) was seen in 2 subjects on intrathecal opioids
254 (12%) vs none on oral opioids and 1 control subject (6%) [24].

255 **Testosterone replacement** (Supplementary Table S6)

256 Six studies described the effect of testosterone replacement among 280 patients with opioid-related
257 hypogonadism. Of these, 5 studies demonstrated an increase in serum testosterone following
258 testosterone administration [35-39]. Patients on testosterone replacement reported improved
259 sexual function [35, 39, 40], sexual desire [36], and mental quality of life [35] as compared to
260 placebo. One study showed that patients with opioid exposure-related hypogonadism who received
261 testosterone replacement had a lower reduction of bone mineral density (T-scores) compared to
262 patients receiving placebo [-0.73 (SD 0.13) vs -1.61 (SD 0.23)] [37].

263 **Discussion**

264 The results of this meta-analysis indicate that hypogonadism is present among approximately 63% of
265 male patients on chronic opioids, while hypocortisolism is present in 15-24% of patients of both
266 genders. In addition, hyperprolactinemia was a common feature in chronic opioid users. No definite
267 conclusions can be drawn on the effects on the somatotropic and HPT axes.

268 Our results are in line with other smaller reviews, reporting on the effects of opioids on the
269 endocrine system [41-46]. As nearly all studies on opioid exposure-related hypogonadism included
270 male patients, a definitive conclusion on the prevalence of opioid exposure-related hypogonadism
271 among female patients cannot be drawn. It is plausible to assume that opioid exposure-related
272 hypogonadism may also be present in women, as opioids suppress gonadal hormone secretion in
273 both animals and humans via a central mechanism [11]. Besides the inhibitory effect of opioids on
274 the gonadal axis, our study showed that the likelihood of gonadotroph deficiency differed between
275 the various opioids and this was highest after fentanyl exposure. The likelihood of developing
276 hypogonadism also appeared to increase when long-acting opioids or higher dosages were used.

277 In addition to the effects on the gonadal axis, we also found an inhibitory effect of opioids on
278 cortisol levels. This is of particular interest, as untreated adrenal insufficiency can result in severe
279 morbidity and, in case of an untreated Addisonian crisis, even death. Patients with diagnosed
280 adrenal insufficiency receive higher stress doses of glucocorticoid replacement in stressful
281 circumstances. Some of these circumstances are illness and severe pain. As opioids are mainly
282 subscribed to cancer pain and non-cancer pain patients, not diagnosing adrenal insufficiency can be
283 particularly harmful. In contrast to our findings, two studies described higher ACTH concentrations,
284 and (hair) cortisol in opioid-treated patients compared to controls [16, 17]. The higher levels of ACTH
285 might be caused by increased chronic stress, anxiety and depression amongst patients who were on
286 methadone maintenance treatment since it has been shown that patients on methadone
287 maintenance treatment had higher levels of ACTH compared to controls [17]. In accord with our
288 results, a study comparing long-term opioid users to age- and sex-matched controls found that
289 22.5% of the opioid users failed on an ACTH- or metyrapone stimulation test, with a higher incidence
290 of insufficiency with higher dosages of opioids, whereas test results were normal in all controls [47].
291 Regarding quality of life, opioid users reported a worse quality of life compared to controls on the
292 physical, social, and emotional role functioning, bodily pain, vitality and mental health domains of

293 the Short-Form 36 (SF-36). The inhibitory effect of opioids on the gonadal and HPA axes is reported
294 to be reversible when the opioid dose is tapered, or when opioid therapy is abrogated [2].

295 There is insufficient evidence for a clear effect of opioids on the activity of the HPT- and
296 somatotropic axes. Animal studies show that acute administration of morphine increases TSH levels
297 after stimulation with TRH [2]. Devilla *et al.* reported a prompt increase in TSH after morphine
298 administration in humans as well [15]. However, amongst chronic opioid users no difference has
299 been found in TSH or fT4 levels compared to controls [2]. Regarding the somatotropic axis, animal
300 studies showed stimulated GH secretion after short-term administration of opioids [48]. However,
301 after long-term administration of opioids, there was no difference in IGF-I levels or in GH-secretion
302 during dynamic testing [49].

303 Data on the interaction between the different axes are lacking. This may be of interest as the
304 gonadal axis is impaired and prolactin levels are raised in opioid users. As prolactin inhibits the cyclic
305 release of GnRH in the hypothalamus, this is an additional explanation of the occurring
306 hypogonadism to direct inhibition of GnRH release by opioids [9].

307 **Strengths and limitations**

308 A major strength of this study is that this is the first study performing a meta-analysis on this topic.
309 This provides a more accurate estimation of the percentage of opioid exposure-related
310 hypogonadism and cortisol deficiency, compared to other studies, which have only reviewed studies
311 on this topic. Our results were supported by the sensitivity analysis, which yielded similar results as
312 those of the main analysis. The studies in this sensitivity analysis have mainly been selected on the
313 most reliable endocrine testing. These analyses resulted in prevalence in the upper range of what
314 has been previously reported in reviews [2, 9, 50] and stress the importance of thorough
315 endocrinological examination of opioid users. A further strength is our comprehensive approach, as
316 this is the first systematic review that assesses all relevant studies on the activity of the gonadal,
317 HPA-, HPT- and somatotropic axes, and on prolactin secretion. Therefore, we were able to give a

318 better understanding of what is known and unknown about this subject. Moreover, we have
319 incorporated studies concerning treatment with hormone substitution therapy and their effects on
320 symptomatology. This study has revealed a lack of data on the female gonadal, the somatotroph and
321 the thyrotroph axes. Moreover, we report a near absence of clinical data in this field.

322 Our study does have some limitations. While we included studies on the effects of opioid use on all
323 pituitary axes, we were able to analyze only the results on the effects on testosterone and cortisol
324 secretion through meta-analysis, due to the limited number of studies reporting on the percentage
325 of patients with endocrine effects for the other hypothalamo-pituitary-end hormone axes.
326 Furthermore, the heterogeneity between studies may have affected the robustness of our results.
327 This heterogeneity is most prominent in the type of opioid used and the included study population
328 between studies. For example, the effect of methadone on the gonadotropic axis seems to be larger
329 than the effect of buprenorphine in several studies comparing the two [25, 51, 52]. Although most
330 reports were in pain patients (both cancer and non-cancer), there were also studies on patients on
331 maintenance treatment for addiction, patients addicted to recreational opioids (heroin, kratom),
332 and healthy volunteers. However, the results of our systematic review showed no difference in the
333 effects of opioids on the endocrine system between different populations. Additionally, the duration
334 of opioid exposure, the method of endocrine assessments, and definitions of endocrine deficiency
335 differed between studies, which may affect the reported outcomes. Although not possible for this
336 meta-analysis due to the heterogeneity of endocrine assessments, studies with the same endocrine
337 assessments and same cut-off values should preferably be analyzed together to obtain more
338 homogenous results. Also, because of the limited number of longitudinal studies, an interaction of
339 the different endocrine axes could not be assessed. Finally, publication bias cannot be excluded,
340 especially in intervention studies.

341 **Clinical implications and future research**

342 Based on the results of this meta-analysis, periodic evaluation of the gonadal axis **in males** and
343 adrenal axis is advisable when patients are exposed to long-term exogenous opioids and this should
344 be included in international guidelines on opioid use. Future studies should focus on the relationship
345 between biochemical alterations indicating possible hormone deficiencies and experienced
346 symptoms, using, amongst others, patient reported outcomes which measure the actual impact on
347 patients' lives **next to the time course of this symptomatology**. Additionally, the added value of
348 screening for these deficiencies and their possible treatment should be assessed, as with the opioid
349 epidemic we currently face, this might pose a tremendous (economic) burden on healthcare systems
350 worldwide. Attention should also be given to hypogonadism in female patients and on the HPT and
351 somatotrophic axes, and prolactin secretion in both sexes, as we currently lack data on these areas.

352 **Data availability**

353 Search strategy, MOOSE-checklist, a list of all included articles, risk of bias assessment guide, results
354 of the risk of bias assessment, and data supplemental tables are made available in a data repository.

355 **Author contributions:**

356 FdV and MB had full access to all of the data in the study and take responsibility for the integrity of
357 the data and the accuracy of the data analysis. Concept and design: AHZN, NK, NRB, OMD.
358 Acquisition or analysis of data: FdV, MB, AHZN. Interpretation of data: FdV, MB, AHZN, NRB, AMP,
359 NK, OMD, DJL, WRvF. Risk of bias assessment: FdV, MB, OMD. Drafting of the manuscript: FdV, MB.
360 Construction of tables and figures: FdV, MB. Critical revision of the manuscript for important
361 intellectual content and gave permission for submission of the final draft: AHZN, NRB, AMP, NK,
362 OMD, DJL, WRvF. Statistical analysis: MB, AHZN. Administrative, technical, or material support: JWS.
363 Supervision: AHZN, AMP, NRB.

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495

496 **Legends for figures and tables**

497 *Figure 1. Selection and screening of studies*

498 *Table 1. Characteristics of the studies included in the meta-analyses.*

499 *Figure 2. Pooled percentage and sensitivity analysis, only including low risk of bias studies, of opioid exposure-*
500 *related hypogonadism. It is important to note that 99.5% of the analyzed patients were males.*

501 *Figure 3. Pooled percentage and sensitivity analysis, only including studies using ITT as assessment of the HPA-*
502 *axis, of opioid exposure-related hypocortisolism*