**Opioids and their endocrine effects: systematic review and meta-analysis**

**Table of contents supplemental files**

Contents

[**Table S1. Characteristics of studies on the opioid effects on the gonadal axis** 2](#_Toc14378782)

[**Table S2. Characteristics of studies on the opioid effects on the HPA-axis** 8](#_Toc14378783)

[**Table S3. Characteristics of studies on the opioid effects on the HPT-axis** 11](#_Toc14378784)

[**Table S4. Characteristics of studies on the opioid effects on prolactin secretion** 12](#_Toc14378785)

[**Table S5. Characteristics of studies on the opioid effects on the somatotropic axis** 13](#_Toc14378786)

[**Table S6. Characteristics of studies reporting on the effect of testosterone supplementation in opioid induced hypogonadism** 14](#_Toc14378787)

[**Table S7. Risk of bias assessment of the included studies** 15](#_Toc14378788)

[**Supplemental document 1: Search strategy** 18](#_Toc14378789)

[**Supplemental document 2: Risk of bias assessment guide** 24](#_Toc14378790)

[**Supplemental document 3: List of included articles** 25](#_Toc14378791)

# **Table S1. Characteristics of studies on the opioid effects on the gonadal axis**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study characteristics** | | | **Patient characteristics** | | | | | **Outcomes** | | | |
| **First Author**  **(publication year)** | **Study design** | **Study period (years)** | **Study population** | **Number of patients**  **N** | **Age in years**  **(mean ± SD)** | **Male**  **N (%)** | **Type of opioid used** | **Axis evaluation** | **Effect of opioid on axis** | **Prevalence of axis deficiency**  **N (%)** | **Duration of follow-up** |
| Singh (2018) | Cross-sectional (non-consecutive) | 2016 | Regular kratom users | 19 | 30.0 (SD 5.6) | 19 (100%) | kratom | Low-dose (3 glasses/day) vs high-dose (>3 glasses/day)  FSH  LH  Testosterone | 4.8 vs 5.9 mU/L  3.0 vs 4.6 mU/L  4.7 vs 5.0 ng/mL | NR | 0 |
| Yee (2018) | Cross-sectional (non-consecutive) | 2015 - 2016 | Patients on opioid maintenance treatment | 76 MMT | 43.3 (SD 10.32) | 107 (100%) | methadone, buprenorphine | MMT vs BMT  Testosterone | 11.7 vs 16.94 nmol/L (p=0.002) | 31 (29)  (total testosterone <8.4nmol/L) | 0 |
| 31 BMT | 41.87 (SD 9.76) | 31 (100%) | 7 (23) |
| Lehtihet (2018) | Placebo controlled trial (non-consecutive) | NR | Healthy male volunteers | 15 | (range 18-45) | 15 (100%) | codeine | Baseline vs after 3 days of codeine  FSH  LH  Testosterone | No difference  No difference  15 (range 10-23) vs 12 (range 4.3-20)nmol/L (p=0.0002) | NR | NR |
| Rubinstein (2017) | Retrospective observational  (consecutive) | 2007-2011 | Males on opioid therapy for non-cancer pain | 1159 | NR | 1159 (100%) | Codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone | OR for androgen deficiency (total testosterone <250ng/dL) in different opioids as compared to hydrocodone  OR for long acting opioids as compared to short-acting | Fentanyl 25.73  Methadone 7.33  Oxycodone 3.15  Long-acting 3.09 (NS) | 451 (39) | 0 |
| Merdin (2016) | Retrospective observational (non-consecutive) | 2009-2013 | Cancer pain patients on opioids | 20 | median: 50 (range 24-72) | 13 (65%) | morphine equivalent daily dose (MEDD) | Correlation of MEDD with serum levels of hormones | Significant negative correlation of testosterone (p=0.040) and free testosterone (p=0.041) levels with MEDD | 11/16 (69) | 9,4 months (median) |
| Gerra (2016) | Cross sectional (non-consecutive) | 2010-2012 | Men on methadone maintenance treatment | 40 opioid users | 34.5 | 40 (100%) | methadone | Serum levels opioid vs controls Testosterone | 419.13 (SD 117.08) vs 576.65 (SD 184.61) (p<0.0001) | NR | NR |
| 40 controls | 35.8 | 40 (100%) |
| Valverde-Filho (2015) | Prospective observational (non-consecutive) | NR | Non-cancer pain patients | 19 controls | 41.84 (SD 8.02) | NR | morphine | Number of patients with a low serum testosterone (total testosterone <271ng/dL) | NR | (17) | NR |
| 12 intrathecal opioid users | 45.19 (SD 9.36) | 7 (58) |
| 10 oral opioid users | 43.05 (SD 8.50) | 7 (70) |
| Rubinstein (2014) | Retrospective observational (consecutive) | 2007-2011 | Men on continuous opioid use | 616 long acting opioid users | Median: 54 (IQR: 46-61) | 616 (100%) | Short- (effect <8 hours) vs long-acting (effect >8hours) opioids | OR for androgen deficiency (total testosterone <250ng/dL) long-acting as compared to short-acting opioids | 3.39 (95%CI 2.39-4.77) | 351 (57) | NR |
| 969 short acting opioid users | Median: 54 (IQR: 46.5-61) | 969 (100%) | 340 (35) |
| Kim (2014) | Cross sectional (consecutive) | 2013 | Non-cancer pain patients on intrathecal opioid | 16 | 60.25 (range 46-85) | 8 (50%) | opioid intrathecal | Testosterone (men)  DHEA (women) | 267.5 (range 23-800) ng/dL  38.75 (range 3-120) ng/dL) | 8 (50)  (4/8 men and 4/8 women) | NR |
| Duarte (2013) | Retrospective observational (consecutive) | 2010 | Male chronic non-cancer patients on intrathecal opioids | 20 | Median 58 (range 47-69) | 20/20 | morphine | Median levels  Testosterone  LH (ref 2.2-13.3IU/L)  FSH (ref 1-7U/L)  Bone density (T-score) (ref -1.0-1.0) | 4.95 (range 1.2-18.8pmol/L)  1.9 (range 0.2-19.9IU/L)  5.3 (range 0.3-23.9IU/L)  -1.10 ( range-3.1-1.0SD) | 17 (85)  (total testosterone < 8pmol/L) | NR |
| Deyo (2013) | Cross-sectional (non-consecutive) | 2004 | Men with back pain | 11327 | 48.6 | 11327 (100%) | short/long acting opioids (morphine equivalents) | OR for the need of opioid replacement  No vs acute vs episodic vs chronic use  MEDD <20 vs 20-120 vs >120  Short- vs long-acting opioids | 1.00 vs 1.02 vs 0.83 vs 1.45 (p=0.007)  1.00 vs 1.01 vs 1.58 (p=0.09)  1.00 vs 0.90 (p=0.5) | NR | NR |
| Sunchatawirul (2012) | Cross-sectional (non-consecutive) | 2007-2008 | HIV infected Thai men | 491 | median 37 (range 34-44) | 491 (100%) | methadone | Methadone users in hypogonadism vs non-hypogonadism group  (free testosterone <225nmol/L) | 9/123 (7.3%) vs 5/368 (1.4%) (p=0.002) | NR | NR |
| Monroe (2012) | Retrospective observational (non-consecutive) | 2001-2004 | Injection drug users | 175 | median 43.8 (IQR 38.7-48.0) | 175 (100%) | methadone | Methadone users in low testosterone vs normal testosterone group  (free testosterone <52pg/mL) | 17/43 (39.5%) vs 20/132 (15.2%) (p=0.001) | NR | NR |
| Hosseini (2012) | Prospective observational (consecutive) | 2009-2011 | Men seeking healthcare for prostate cancer screening and LUTS | 56 opium users | NR | 56 (100%) | NR | Serum levels opioid vs controls Testosterone  LH  FSH | 339.08 (SD 142.49) vs 396.71 (SD 133.64) ng/dL (p=0.008)  6.68 (SD 5.78) vs 6.79 (SD 5.87) IU/L (p=0.890)  8.16 (SD 4.945) vs 8.61 (SD 4.29) IU/L (p=0.429) | 29 (52)  (total testosterone <300ng/dL) | NR |
| 82 controls | 82 (100%) | 25 (30) |
| Wong (2011) | Prospective observational (non-consecutive) | 2008-2009 | Chronic pain patients | 73 opioid users | Men 55 (range 29-77) Women 53 (range 28-83) | 26 (36%) | opioids (morphine equivalent daily dose) | Serum levels opioid vs controls  Men:  Free testosterone  Total testosterone  LH  Women:  Free testosterone  Total testosterone  Oestradiol  LH  FSH | 20.2 (SD 2.6) vs 30.2 (SD 5.0)pmol/L (p=0.12)  8.6 (SD 0.9) vs 10.7 (SD 2.1) nmol/L (p=0.40)  4.8 (SD 0.6) vs 5.3 (SD 0.6) U/L (p=0.11)  1.3 (SD 0.1) vs 2.3 (SD 0.2) pmol/L (p=0.02)  0.9 (SD 0.1) vs 1.2 (SD 0.1) nmol/L (p=0.09)  154.6 (SD 36.8) vs 145.3 (SD 25.0) (p=0.74)  18.8 (SD 3.3) vs 15.3 (SD 2.1) U/L (p=0.75)  33.7 (SD 5.5) vs 30.8 (SD 6.0) (p=0.94) | 20/26 men (77) | NR |
| 24 controls | Men 52 (range 36-70)  Women 55 (range 25-84) | 6 (25%) | 2/6 men (33) |
| Skipworth (2011) | Cross-sectional (non-consecutive) | NR | Unresectable pancreatic cancer patients | 43 opioid users | Men median 67 (range 43-94)  Women median 69 (range 50-91) | 25 (58%) | several opioids (MEDD) | Serum levels opioid vs controls Men:  Total testosterone  Free testosterone  LH  FSH  Postmenopausal women:  Free testosterone  Total testosterone  Oestradiol  LH  FSH | 5.8 vs 13.8 nmol/L (p<0.001)  0.058 vs 0.187 nmol/L (p<0.001)  3.8 vs 4.7 U/L (p=0.019)  4.6 vs 7.3 U/L (p=0.054)  1.0 vs 0.9 nmol/L (p=0.957)  0.009 vs 0.008 nmol/L (p=0.967)  76.0 vs 75.0 pmol/L (p=0.759)  0.9 vs 23.9 U/L (p=0.033)  2.1 vs 65.6 U/L (p=0.030) | NR | NR |
| 124 controls | Median 69 (range 56-86) | 65 (52%) |
| Rhodin (2010) | Prospective observational (non-consecutive) | 2002-2009 | Chronic non-cancer pain on long term strong opioids | 39 opioid users | 48 (range 32-63) | 15 (38%) | several opioids | Serum levels opioid vs controls Men:  Testosterone  LH  LH after GnRH  FSH  FSH after GnRH  Females <50:  Estradiol  LH  LH after GnRH  FSH  FSH after GnRH  Females >50:  Estradiol  LH  LH after GnRH  FSH  FSH after GnRH | 5.56 (SEM 1.16) vs 15.5 (SEM 2.06) nmol/L (p=0.001)  1.11 (SEM 0.27) vs 6.42 (SEM 1.5) IE/L (p=0.01)  7.91 (SEM 1.47) vs 25.5 (SEM 4.18) IE/L (p=0.01)  2.08 (SEM 0.51) vs 8.16 (SEM 2.41) IE/L (p=0.05)  4.31 (SEM 0.89) vs 13.1 (SEM 3.76) IE/L (p=0.053)  208 (SEM 73.2) vs 510 (SEM 98.3) pmol/L (p=0.05)  3.71 (SEM 0.88) vs 6.74 (SEM 2.07) IE/L (NS)  17.6 (SEM 4.85) vs 38.0 (SEM 2.64) IE/L (p=0.01)  4.72 (SEM 0.97) vs 6.50 (SEM 3.32) IE/L (NS)  12.2 (SEM 2.6) vs 16.0 (SEM 4.5) IE/L (NS)  49.0 (SEM 6.81) vs 60.5 (SEM 15.6) pmol/L (NS)  14.0 (SEM 5.58) vs 34.6 (SEM 11.5) IE/L (NS)  54.9 (SEM 20.8) vs 154 (SEM 66.4) IE/L (NS)  25.7 (SEM 9.8) vs 60.7 (SEM 11.3) IE/L (NS)  49.2 (SEM 17.1) vs 94.2 (SEM 17.7) IE/L (p=0.055) | 12/15 men (80)  (sexual dysfunction and low testosterone) | NR |
| 20 controls | 49 (range 32-63) | 8 (40%) | 2/8 men (25) |
| Fraser (2009) | Prospective observational (consecutive) | 2005-2006 | Chronic non cancer pain patients on opioids | 26 | Men 45.4 (SD 5.5) | 12 (46%) | opioids (morphine equivalent doses) | Men:  LH  FSH  total testosterone  free testosterone  Women:  LH  FSH  estradiol  progesterone | 2.2 (SD 1.4) IU/L (ref 1.5-9)  3.6 (SD 1.4) IU/L (ref 1-18)  6.9 (SD 4.2) nmol/L (ref 9.1-55)  19.3 (SD 12.7) pmol/L (ref 18-144)  6.9 (SD 7.0) IU/L (ref 0.5-76)  6.3 (SD 5.3) IU/L (ref 2-33)  356 (SD 374) pmol/L (ref 121-1930)  18 (SD 29) nmol/L (ref 0.5-89) | 10/12 (83) men hypogonadism  (free testosterone <18pmol/L)  6/12 (50) men osteopenia  3/14 (21) women osteopenia | NR |
| Women 38.6 (SD 7.2) |
| Hallinan (2009) | Prospective observational (consecutive) | 2003 | Men on opiate maintanance treatment | 79 MMT | 38.3 (SD 8.2) | 84 (100%) | methadone | Mean levels vs matched controls  Total testosterone  Free testosterone  Estradiol  FSH  LH | 11.4 (SD 7.0) vs 18.9 (SD 6.1) nmol/L (p<0.0001)  28.6 (22.6) vs 58.6 (SD 18.6) pmol/L (p<0.0001)  71.7 (SD 51.8) vs 148.4 (SD 62.1) pmol/L (p<0.0001)  3.9 (SD 2.7) vs 3.9 (SD 1.7) U/L (NS)  3.9 (SD 2.1) vs 7.2 (SD 3.1) U/L (p<0.0001) | 51 (65)  (total testosterone < 12nmol/L) | NR |
| 18 BMT | 35 (SD 5.6) | 19 (100%) | buprenorphine | Total testosterone  Free testosterone  Estradiol  FSH  LH | 18.9 (SD 8.8) vs 19.3 (SD 6.6) nmol/L (NS)  44.5 (SD 37.9) vs 61.0 (SD 20.0) pmol/L (p=0.0128)  78.9 (SD 58.0) vs 158.5 (SD 61.5) pmol/L (p<0.0001)  4.3 (SD 1.9) vs 3.9 (SD 1.8) U/L (NS  4.0 (SD 2.3) vs 6.9 (SD 3.2) U/L (p=0.0004) | 5 (28) |
| Daniell (2008) | Prospective observational (non-consecutive) | 2003-2006 | Female non-cncer pain patients on opioids | 47 opioid users | Intact ovary: 45.9 (SD 10.6) Post oophorectomy: 52.9 (SD 10.7) | 0 | Several opioids | Mean levels vs controls  Ages 30-50  Total testosterone  Free testosterone  Estradiol  DHEAS  Ages 51-75  Total testosterone  Free testosterone  Estradiol  DHEAS | 30.7 (SD 21.5) vs 54.4 (SD 10.3) ng/dL (p<0.001)  4.0 (SD 3.5) vs 7.0 (SD 2.4) PG/Ml (P<0.01)  63.2 (SD 56.7) vs 132.3 (SD 108.1) pg/mL (p<0.05)  51.2 (SD 52.1) vs 113.3 (SD 53.7) µg/dL (p<0.01)  24.6 (SD 16.6) vs 36.7 (SD 17.7) ng/dL (NS)  3.9 (SD 2.3) vs 5.8 (SD 3.9) pg/mL (p<0.04)  18.7 (SD 9.3) vs 29.7 (SD 25.2) pg/mL (NS)  33.9 (SD 24.6) vs 66.5 (SD 41.3) ug/dL (p<0.02) | NR | NR |
| 68 controls | Intact ovary: 53.9 (SD 11.2)  Post oophorectomy: 60.3 (SD 9.6) | 0 |
| Shahramian (2006) | Case control study (non-consecutive) | 2004 | Opium dependents | 56 opium dependents | 25 (SD 5) | 28 (50%) | opium | Mean levels vs controls  Men  Testosterone  LH  FSH  Premenopausal women  LH  FSH  Estradiol  Progesterone  Postmenopausal women  LH  FSH  Estradiol  Progesterone | 5.5 (SD 4.9) vs 16 (SD 4) nmol/L (p<0.001)  1.3 (SD 0.9) vs 5.3 (SD 3.3) U/L (p<0.001)  4.3 (SD 2) vs 6.0 (SD 3.9) U/L (NS)  2.1 (SD 186) vs 14 (SD 13.2) U/L (NS)  6.0 (SD 5.0) vs 8.9 (SD 8.5) U/L (NS)  130 (SD 118) vs 356 (SD 390.3) pmol (NS)  2 (SD 2.3) vs 8.6 (SD 11.0) pmol (NS)  4.1 (SD 3.6) vs 27.0 (SD 13.8) U/L (p<0.001)  15.0 (SD 16.4) vs 37 (SD 21.3) U/L ((p=0.015)  105 (SD 116.7) vs 55.9 (SD 37.4) pmol (NS)  1.3 (SD 0.7) vs 1.6 (SD 0.4) pmol (NS) | NR | NR |
| 56 controls | 25 (SD 5) | 28 (50%) |
| Bliesener (2005) | Cross-sectional (non-consecutive) | NR | Male heroin addicts on maintenance treatment | 17 BMT | 34.7 (SD 7.4) | 17 (100%) | methadone | Mean levels MMT vs BMT vs controls  Testosterone  Free testosterone  Estradiol  LH  FSH | 2.8 (SD 1.2) vs 5.1 (SD 1.2) vs 4.9 (SD 1.3) ng/mL (p<0.0001)  7.8 (SD 2.9) vs 17.1 (SD 4.8) pg/mL (p<0.0001)  25 (SD 9) vs 29 (SD 10) pmol/L (NS)  3.8 (SD 2.7) vs 4.4 (SD 1.6) vs 4.0 (SD 1.3) U/L (NS)  3.8 (SD 2.7) vs 4.3 (SD 2.3) vs 3.9 (SD 2.0) U/L (NS) | NR | NR |
| 37 MMT | 37.5 (SD 6.9) | 37 (100%) | buprenorphine |
| 51 controls | 35.2 (SD 4.5) | 51 (100%) |  |
| Rajagopal (2004) | Prospective observational (non-consecutive) | 2001-2003 | Male cancer survivors with opioid treatment | 20 opioid users | median 51 (SD 11.3) | 20 (100%) | several opioids (MEDD) | Median levels opioid vs controls  Testosterone  FSH  LH | 5.0 (range 0.7-13.2) vs 13.8 (range 5.9-33.9) nmol/L (p<0.0001)  2.85 (range 0.7-28.6) vs 5.3 (range 1.8-23.6) IU/L (p=0.084)  1.8 (range 0.5-6.9) vs 4.2 (range 1.9-9.9) IU/L (p=0.0014) | 18 (90) (total testosterone <21nmol/L) | NR |
| 20 matched controls | Median 58 (SD 13.7) | 20 (100%) | 8 (40) |
| Daniell (2002) | Cross sectional (non-consecutive) | NR | Male opioid consumers | 54 opioid users | 49.9 (range 30-78) | 54 (100%) | several opioids (MEDD) | Subnormal testosterone  (based on age adjusted FT/TT ratio) | NR | 40 (74) | NR |
| 27 controls | 57.4 (range 40-67) | 27 (100%) | 2 (8) |
| Roberts (2002) | Prospective observational (consecutive) | NR | Men with non-cancer pain on intrathecal opioids | 10 | 52 (SD 4, range 25-64) | 10 (100%) | intrathecal morphine | Mean levels at baseline vs after 1, 4, 12 weeks Testosterone  LH  FSH | 7.7 (SEM 1.1) vs 2.0 (SEM 0.7) vs 2.8 (SEM 0.5) vs 4.0 (SEM 0.9) nmol/L (p<0.0001)  3.3 (SEM 0.5) vs 2.3 (SEM 0.7) vs 1.8 (SEM 0.3) vs 3.0 (SEM 0.6) U/L (NS)  4.6 (SEM 0.5) vs 2.5 (SEM 0.2) vs 3.2 (SEM 0.3) vs 3.8 (SEM 0.4) U/L (p<0.0001) | NR | 12 weeks |
| Abs (2000) | Retrospective observational (non-consecutive) | NR | Non-cancer pain patients on intrathecal opioids | 73 opioid users | 49.2 (SD 11.7) | 29 (40%) | intrathecal morphine, hydromorphone | Men:  Testosterone  LH  FSH  Premenopausal women:  LH  FSH  Estradiol  Progesterone  Postmenopausal women:  LH  FSH  Estradiol  Progesterone | 6.9 (SD 5.2) vs 15.4 (SD 4.4) nmol/L (p<0.001)  1.7 (SD 1.4) vs 4.3 (SD 2.1) U/L (p<0.001)  4.7 (SD 2.6) vs 5.7 (SD 4.4) U/L (NS)  2.7 (SD 2.6) vs 12.4 (SD 14.2) U/L (NS)  6.4 SD 5.6) vs 9.4 (SD 9.2) U/L (NS)  127.0 (SD 124.0) vs 383.3 (SD 404.6) pmol/L (NS)  1.6 (SD 2.6) vs 8.6 (SD 13.7) nmol/L (NS)  3.3 (SD 3.3) vs 27.7 (SD 14.1) U/L (p<0.001)  14.6 (SD 17.6) vs 39.8 (SD 22.7) U/L (p=0.012)  100.2 (SD 122.6) vs 55.8 (SD 33.6) pmol/L (NS)  1.0 (SD 0.6) vs 1.0 (SD 0.6) nmol/L (NS) | 25/29 men (86)  (total testosterone <9nmol/L) | mean 26.6 (SD 16.3) months |
| 20 controls | 54.2 (SD 14.0) | 11 (55%) |
| Ambrosi (1986) | Prospective trial (non-consecutive) | NR | Addinson disease patients | 8 | Men (range 40-52) | 3 (38%) | loperamide | Basal value vs 300 min post-loperamide  LH (Men)  LH (Women) | 19.7 (SEM 5.0) vs 18.7 (SEM 5.0) mIU/mL (NS  87.8 (SEM 17.2) 77.5 (SEM 11.2) mIU/mL (NS)) | NR | NR |
| Women (range 20-71) |

NR: not reported, SEM: standard error of the mean, CI: confidence interval

# **Table S2. Characteristics of studies on the opioid effects on the HPA-axis**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study characteristics** | | | **Patient characteristics** | | | | | **Outcomes** | | | |
| **First Author**  **(publication year)** | **Study design** | **Study period (years)** | **Study population** | **Number of patients** | **Age in years**  **(mean ± SD)** | **Male**  **N (%)** | **Type of opioid used** | **Axis evaluation** | **Effect of opioid on axis** | **Prevalence of axis deficiency**  **N (%)** | **Follow-up** |
| Peeters (2017) | Retrospective observational (non-consecutive) | NR | ICU patients | 156 | 66 (SEM 1.1) | 103 (66%) | morphine, alfentanil, fentanyl, sulfentanil, tramadol, piritramide | ACTH, morning cortisol | Cortisol: decrease of 8.6 (95%CI 3.6-13.6) nmol/L for every 10mg morphine equivalent (p=0.001) | NR | 3 days |
| 20 | 58 (SEM1.1) | 11 (55%) |
| Gibb (2016) | Prospective observational (non-consecutive) | NR | Chronic pain patients on long-term opioid analgesia | 48 | 53.5 (95%CI 45.4-62.4) | 25 (52%) | tramadol, oxycodone, morphine sulfate, dihydrocodeine, fentanyl/buprenor-phine patch | Morning cortisol, ACTH-test | 10% High dose opioid users suboptimal cortisol response on ACTH | 4 (9)  (morning cortisol <100nmol/L, 3 (6) ACTH-test peak <430noml/L) | No follow-up |
| Merdin (2016) | Retrospective observational (non-consecutive) | 2009-2013 | Cancer pain patients on opioids | 20 | median: 50 (range 24-72) | 13 (65%) | several opioids (morphine equivalent) | ACTH, morning cortisol | No significant correlation between MEDD and cortisol | 3 (15) (morning cortisol <4.3µg/dL) | 9,4 months (median) |
| Yang (2016) | Prospective observational (non-consecutive) | NR | Former heroin addicts on MMT | 52 MMT | 40.6 (SD 6,2) | 52 (100%) | methadone, buprenorphine | MMT vs control  Hair cortisol concentration | 10.0 (0.96-68.5) pg/mg vs 6.45 (1.43-28.0) pg/mg, p=0.046 | NR | NR |
| 41 controls | 42.2 (SD 12,2) | 41 (100%) |
| Kershaw (2015) | Prospective observational (non-consecutive) | NR | Healthy young Caucasian adults | 30 intervention | 21.9 (SD 0.5) | 18 (60%) | oxycodone, immediate release | Salivary cortisol concentration 6 hours after oxycodone vs control | No significant difference | NR | 6 hours |
| 19 controls | 22.3 (SD 0.8) | 12 (63%) |
| Nenke (2015) | Prospective observational (non-consecutive) | 2012-2014 | Chronic pain patients on long-term opioid analgesia | 7 opioid users | 71 (SD 4) | 7 (100%) | several opioids (morphine equivalent) | Opioid vs controls  Waking salivary cortisol  ACTH-test | 20% lower in opioid users (NS)  Lower values in opioid users (NS) | NR | NR |
| 19 controls | 71 (SD 6) | 19 (100%) |
| Valverde-Filho (2015) | Prospective observational (non-consecutive) | NR | Non-cancer pain patients | 18 controls | 41.84 (SD 8.02) | NR | morphine | 24-hour urinary cortisol, ITT cortisol peak | NR | 4 (22)  (ITT cortisol-peak <18µg/dL) | NR |
| 18 intrathecal opioid users | 45.19 (SD 9.36) | 6 (33) |
| 18 oral opioid users | 43.05 (SD 8.50) | 9 (50) |
| Gerber (2012) | RCT  (non-consecutive) | NR | Male patients on diacetylmorphine maintenance treatment | 28 | 41.3 (SD 6.6) | 28 (100%) | diacetylmorphine | 20 minutes after injection of opioid vs control  Serum cortisol  Salivary cortisol  Serum ACTH | Significant reduction in all parameters (p<0.0001) | NR | NR |
| Aloisi (2011b) | Cross sectional (non-consecutive) | 2009-2010 | Noncancer pain patients | 85 opioid users | Opioid women: 52.74 (SD 11.97, range 30-77) | 14 (16%) | fentanyl, oxycodone, tramadol, codeine, morphine, hydromorphone | Opioid vs controls ACTH,  Morning cortisol | Decreased ACTH (p<0.001)  Decreased cortisol (p<0.04) | NR | NR |
| 85 age matched controls | Opioid men: 54.08 (SD 10.47, range 45-75) | 14 (16%) |
| Rhodin (2010) | Prospective observational (non-consecutive) | 2002-2009 | Chronic non-cancer pain on long term strong opioids | 39 opioid users | 48 (range 32-63) | 15 (38%) | several opioids | Opioid vs controls  Morning cortisol  CRH-test | 429 (SEM 36.9) vs 396 (SEM 30) nmol/L (NS)  610 (SEM 35.2) vs 532 (SEM 23.5) nmol/L (NS) | NR | NR |
| 20 controls | 49 (range 32-63) | 8 (40%) |
| Zhang (2008) | Prospective observational (non-consecutive) | NR | Heroin dependent patients | 30 MMT | 30.7 (SD 5.0) | 25 (83%) | methadone | MMT vs controls  CRH  ACTH  Morning cortisol | 20.20 (SD 13.33) vs 39.43 (SD 13.46) pg/mL (p<0.001)  21.69 (SD 7.36) vs 21.00 (SD 5.70) pg/mL (NS)  9.11 (SD 7.23) vs 17.70 (SD 4.24) µg/dL (p<0.001) | NR | NR |
| 30 controls | 29.2 (SD 5.0) | 23 (77%) |
| Schluger (2003) | Prospective observational (non-consecutive) | NR | Men on methadone maintenance treatment | 8 opioid users | 36.8 (SD 14.3, range 21-55) | 8 (100%) | methadone | MMT vs controls  CRF-stimulated ACTH  Serum cortisol | Significantly higher response in MMT-group  No significant difference | NR | NR |
| 16 controls | 30.2 (SD 6.2, range 20-42) | 16 (100%) |
| Tennant (2002) | Prospective observational (consecutive) | NR | Non-cancer pain patients | 40 | (range 25-60) | 21 (53%) | several opioids (morphine equivalent) | Morning cortisol | NR | 2 (5) (morning cortisol <5µg/dL) | 90 days |
| Stine (2002) | Double blind placebo controlled trial (non-consecutive) | NR | Men on methadone maintenance treatment | 8 opioid users | 38 (SEM 2.6) | 6 (75%) | methadone | Opioid vs controls  Yohombine-stimulated cortisol | Significantly higher cortisol levels after Yohombine administration F score 21.09 p<0.0005 | NR | NR |
| 9 controls | 30 (SEM 3.7) | 9 (100%) |
| Gerra (2001) | Prospective observational (non-consecutive) | NR | Men on methadone maintenance treatment | 20 opioid users | 27.1 (SD 6.5, range 20-33) | 20 (100%) | methadone | ACTH and cortisol after monetary task |  | NR | NR |
| 20 controls | 26.4 (SD 6.5, range 19-32) | 20 (100%) |
| Schluger (2001) | Prospective observational (non-consecutive) | NR | Men on methadone maintenance treatment | 10 opioid users | 32.3 (SD 12.2, range 18.3-55.1) | 8 (80%) | methadone | Opioid vs controls  ACTH after metyrapone  Coritsol after metyrapone | No significant difference  No significant difference | NR | NR |
| 21 controls | 34.1 (SD 7.8, range 22.0-47.4) | 14 (67%) |
| Abs (2000) | Retrospective observational (non-consecutive) | NR | Non-cancer pain patients on intrathecal opioids | 61 opioid users | 49.2 (SD 11.7) | 29 (40%) | intrathecal morphine, hydromorphone | Opioid vs control  ACTH  24-hour urinary cortisol  ITT ACHT-peak  ITT cortisol peak | 20.1 (SD 14.3) vs 16.9 (SD 8.9) ng/L (NS)  193.8 (SD 157.3) vs 202.1 (SD 105.0) ng/L (NS)  135.3 (SD 53.8) vs 160.1 (SD 43.9) µg/L (NS)  245.4 (SD 62.1) vs 300.8 (SD 73.6) µg/L (p=0.002) | 9 (15)  (ITT cortisol-peak <180µg/L) | mean 26.6 (SD 16.3) months |
| 20 controls | 54.2 (SD 14.0) | 11 (55%) | NR |
| Auernhammer (1994) | RCT  (non-consecutive) | NR | Healthy male volunteers | 6 | (range 25-27) | 6 (100%) | loperamide | 180 minutes after loperamide vs baseline ACTH  Cortisol | 2 (SE 0) vs 5 (SE 0) pmol/L (p<0.01)  154 (SE 16) vs 356 (SE 44) nmol/L (p<0.01) | NR | NR |
| Garland (1989) | Prospective trial (non-consecutive) | NR | Healthy male volunteers | 9 | median 23 (range 20-41) | 9 (100%) | codeine | Cortisol 60 minutes after codeine injection | Cortisol levels < 4µg/dL: 8 (89) | NR | NR |
| Ambrosi (1986) | Prospective trial (non-consecutive) | NR | Addinson disease patients | 8 | Men (range 40-52) | 3 (38%) | loperamide | 300 minutes after loperamide vs baseline ACTH | 126 (SEM 33) vs 854 (SEM 167) pg/mL (p<0.001) | NR | NR |
| Women (range 20-71) |
| Cushman (1970) | Prospective observational (non-consecutive) | NR | Men on methadone maintenance treatment | 34 opioid users | (range 23-53) | 34 (100%) | methadone | MMT vs controls ITT 17-OH-cs peak | No significant difference | NR | NR |
| 9 controls | 9 (100%) |

NR: not reported, SEM: standard error of the mean, CI: confidence interval

# **Table S3. Characteristics of studies on the opioid effects on the HPT-axis**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study characteristics** | | | **Patient characteristics** | | | | | **Outcomes** | | |
| **First Author**  **(publication year)** | **Study design** | **Study period (years)** | **Study population** | **Number of patients**  **N (%)** | **Age in years**  **(mean ± SD)** | **Male**  **N (%)** | **Type of opioid used** | **Axis evaluation** | **Effect of opioid on axis** | **Duration of follow-up** |
| Singh (2018) | Cross-sectional  (non-consecutive) | October-December 2016 | Regular kratom users | 19 | 30.0 (SD 5.6) | 19 (100%) | kratom | Serum fT4  low dose vs high dose | 16.2mU/L vs 14.3mU/L | 0 |
| Valverde-Filho (2015) | Prospective observational  (non-consecutive) | NR | Non-cancer pain patients | 17 controls | 41.84 (SD 8.02) | NR | morphine | Number of patients with low ΔTSH (<5µU/mL) | 0/17 | NR |
| 19 intrathecal opioid users | 45.19 (SD 9.36) | 6/19 |
| 18 oral opioid users | 43.05 (SD 8.50) | 6/18 |
| Rhodin (2010) | Prospective observational  (non-consecutive) | 2002-2009 | Chronic non-cancer pain on long term strong opioids | 39 opioid users | 48 (range 32-63) | 15 (38.4%) | several opioids | Opioid vs controls Serum TSH  Serum ft4  TRH-stimulated TSH | 3.95 (SEM 1.29) vs 1.84 (SEM 0.16) (NS)  13.3 (SEM 0.45) vs 12.6 (SEM 0.58) mIE/L (NS) 17.3 (SEM 4.36) vs 12.6 (SEM 1.2) mIE/L (NS) | NR |
| 20 controls | 49 (range 32-63) | 8 (40%) |
| Fraser (2009) | Prospective observational (consecutive) | 2005-2006 | Chronic non cancer pain patients | 12 men | 45.4 (SD 5.5) | 12 | opioids (morphine equivalent doses) | Serum TSH  (ref 0.35-5.0mU/L) | 2.3 (SD 0.9) mU/L | NR |
| 14 women | 38.6 (SD 7.2) | 14 | 1.9 (SD 1.2) mU/L |
| Abs (2000) | Retrospective observational  (non-consecutive) | NR | Non-cancer pain patients on intrathecal opioids | 73 opioid users | 49.2 (SD 11.7) | 29 (39.7%) | intrathecal morphine, hydromorphone | Opioids vs controls Serum fT4  Serum fT3  Serum TSH  TRH-stimulated TSH | 15.4 (SD 2.6) vs 15.9 (SD 3.1) pmol/L (NS)  5.2 (SD 0.7) vs 4.6 (SD 0.7) pmol/L (p=0.001)  1.5 (SD 0.9) vs 1.2 (SD 0.5) mU/L (NS)  8.5 (SD 5.1) vs 8.0 (SD 4.2) mU/L (NS) | mean 26.6 (SD 16.3) months |
| 20 controls | 54.2 (SD 14.0) | 11 (55%) |
| Devilla (1985) | Prospective trial  (non-consecutive) | NR | Hypothyroid patients and healthy volunteers | 7 hypothyroid | (range 41-69 | 2 (28.6%) | morphine | Before vs after morphine  TSH | 46.4 (SE 7.64) vs 64.5 (SE 7.62) uU/L (p<0.01) | NR |
| 10 volunteers | (range 20-45) | 4 (40%) |
| Shenkman (1972) | Prospective observational  (non-consecutive) | NR | Patients on methadone maintenance treatment | 6 | (range 24-50) | 4/6 (66.7%) | methadone | Opioid vs controls TRH, T4, T3, TSH | No significant difference | NR |

NR: not reported, SEM: standard error of the mean, CI: confidence interval

# **Table S4. Characteristics of studies on the opioid effects on prolactin secretion**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study characteristics** | | | **Patient characteristics** | | | | **Outcomes** | | | |
| **First Author**  **(publication year)** | **Study design** | **Study period (years)** | **Study population** | **Number of patients** | **Age in years**  **(mean ± SD)** | **Male**  **N (%)** | **Type of opioid uses** | **Axis evaluation** | **Effect of opioid on axis** | **Duration of follow-up** |
| Merdin (2016) | Retrospective observational (non-consecutive) | 2009-2013 | Cancer pain patients | 20 | Median: 50 (range 24-72) | 13 (65%) | Several opioids: MEDD | Number of patients with abnormal prolactin (ref 4.1-18.4ng/mL) | 0 patients with low prolactin, 8 patients with high prolactin | Median: 9.4 months |
| Valverde-Filho (2015) | Prospective observational (non-consecutive) | NR | Non-cancer pain patients | 19 controls | 41.84 (SD 8.02) | NR | Morphine | Prolactin | No difference between groups | NR |
| 19 intrathecal opioid users | 45.19 (SD 9.36) |
| 19 oral opioid users | 43.05 (SD 8.50) |
| Duarte (2013) | Retrospective observational (consecutive) | 2010 | Male chronic non-cancer patients on intrathecal opioids | 20 | Median: 58 (range 47-69) | 20 (100%) | Morphine | Prolactin | 225 (ref: 0-445) mU/L | NR |
| Wong (2011) | Prospective observational (non-consecutive) | 2008-2009 | Chronic non-cancer pain patients | 73 opioid users | Men: 55 (range 29-77) Women: 53 (range 28-83) | 26 (36%) | Several opioids: MEDD | opioid vs controls  Prolactin | Men: 10.7 (SD: 1.2) vs 5.6 (SD: 0.5) µg/L (p=0.0006) | NR |
| 24 controls | Men: 52 (range 36-70)  Women: 55 (range 25-84) | 6 (25%) | Women: 12.2 (SD: 2.2) vs 14.9 (SD 2.2) µg/L (p=0.61) |
| Rodin (2010) | Prospective observational (non-consecutive) | 2002-2009 | Chronic non-cancer pain patients on long term strong opioids | 39 opioid users | 48 (range 32-63) | 15 (38%) | Several opioids | opioid vs controls  Prolactin | 26.4 (SEM: 3.5) vs 9.5 (SEM: 0.87) µg/L (p=0.001) | NR |
| 20 controls | 49 (range 32-63) | 8 (40%) |
| Abs (2000) | Retrospective observational (non-consecutive) | NR | Non-cancer pain patients on intrathecal opioids | 73 opioid users | 49.2 (SD 11.7) | 29 (40%) | Intrathecal morphine, hydromorphone | opioid vs controls  Prolactin | 6.8 (SD 7.0) vs 4.9 (SD 2.6) µg/L (NS) | mean 26.6 (SD 16.3) months |
| 20 controls | 54.2 (SD 14.0) | 11 (55%) |
| Ambrosi (1986) | Prospective trial (non-consecutive) | NR | Addinson disease patients | 8 | Men (range 40-52) | 3 (38%) | Loperamide | Baseline vs 300 minutes after loperamide  Prolactin | 13.4 (SEM 3.8) vs 16.9 (SEM 4.7) ng/mL (NS) | NR |
| Women (range 20-71) |

NR: not reported, SEM: standard error of the mean, CI: confidence interval, ref: reference range, SD: standard deviation

# **Table S5. Characteristics of studies on the opioid effects on the somatotropic axis**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study characteristics** | | | **Patient characteristics** | | | | **Outcomes** | | | |
| **First Author**  **(publication year)** | **Study design** | **Study period (years)** | **Study population** | **Number of patients**  **N (%)** | **Age in years**  **mean** | **Male**  **N (%)** | **Type of opioid uses** | **Axis evaluation** | **Effect of opioid on axis** | **Duration of follow-up** |
| Merdin (2016) | Retrospective observational (non-consecutive) | 2009-2013 | Cancer pain patients | 20 | median: 50 (range 24-72) | 13 (65%) | Several opioids: MEDD | Number of patients with GH outside reference range  (0-8ng/mL) | 1 patient with high GH | Median: 9.4 months |
| Valverde-Filho (2015) | Prospective observational (non-consecutive) | NR | Non-cancer pain patients | 18 controls | 41.84 (SD 8.02) | NR | Morphine | Number of patients with low IGF-I (-2.0SD)/low ITT GH-peak (<3.2ng/mL) | 5 (28%) / 1 (6%) | NR |
| 18 intrathecal opioid users | 45.19 (SD 9.36) | 5 (28%) / 2 (11%) |
| 18 oral opioid users | 43.05 (SD 8.50) | 8 (44%) /0 |
| Rhodin (2010) | Prospective observational (non-consecutive) | 2002-2009 | Chronic non-cancer pain patients on long term strong opioids | 39 opioid users | 48 (range 32-63) | 15 (38.4%) | Several opioids | Morning GH opioid vs controls | 1.83 (SEM 1.25) vs 2.82 (SEM 1.28) mIE/L (NS) | NR |
| 20 controls | 49 (range 32-63) | 8 (40%) |
| Abs (2000) | Retrospective observational (non-consecutive) | NR | Non-cancer pain patients on intrathecal opioids | 73 opioid users | 49.2 (SD 11.7) | 29 (39.7%) | Intrathecal morphine, hydromorphone | opioid vs controls  Serum IGF-I  ITT GH peak | -0.53 (SD 1.45) vs 0.57 (SD 1.00) SD (p=0.002)  14.5 (SD 12.7) vs 20.9 (SD 11.5) µg/L (p=0.010) | mean 26.6 (SD 16.3) months |
| 20 controls | 54.2 (SD 14.0) | 11 (55%) |
| Ambrosi (1986) | Prospective trial (non-consecutive) | NR | Addinson disease patients | 8 | Men (range 40-52) | 3 (38%) | Loperamide | Baseline vs 300 minutes after loperamide  GH | 1.6 (SEM 0.3) vs 1.8 (SEM 0.1) ng/mL (NS) | NR |
| Women (range 20-71) |

NR: not reported, SEM: standard error of the mean, CI: confidence interval

# **Table S6. Characteristics of studies reporting on the effect of testosterone supplementation in opioid induced hypogonadism**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study characteristics** | | | **Patient characteristics** | | | | **Opioids** | | | |
| **First Author**  **(publication year)** | **Study design** | **Study period (years)** | **Study population** | **Number of patients**  **N** | **Age in years**  **mean** | **Male**  **N (%)** | **Replacement drug** | **Axis evaluation** | **Effect of supplementation on axis** | **Duration of follow-up** |
| Raheem (2017) | Retrospective observational | NR | Men with opioid induced hypogonadism | 27 | 55 (IQR 39-57), 54.4 (IQR 36-58) | 27 | Testosterone | Testosterone vs non-testosterone  Serum testosterone  IIEF score  ADAM score | 497.5 vs 242.2 (p=0.03)  20 vs 12 (p<0.05)  3 vs 7 (p<0.05) | 18 months |
| Huang (2017) | RCT | NR | Men with opioid induced androgen deficiency | 33 on testosterone | 48 (SD 8) | 55 | 5mg transdermal testosterone gel (androgel 1%) | After 14 weeks vs baseline  Serum testosterone  ISI score  PCS score | 775 (SD 555) vs 223 (SD 86) ng/dL  No significant difference as compared to placebo  No significant difference as compared to placebo | 14 weeks |
| 29 on placebo |
| Basaria (2015) | RCT | NR | Men with opioid induced hypogonadism | 36 on testosterone | 48 (SD 9) | 65 | Transdermal testosterone gel (Androgel) | Testosterone vs placebo  Serum testosterone  IIEF score | 790 (SD 544) vs 328 (SD 185) ng/dL (p<0.01)  Significant greater increase in sexual desire in testosterone arm | 14 weeks |
| 29 on placebo | 50 (SD 6) |
| Finch (2015) | Prospective observational | NR | Men with opioid induced hypogonadism on intrathecal opioids | 11 on testosterone | 57.7 (SD 3.5) | 27 | testosterone enanthate depot | Testosterone vs placebo  Serum testosterone  Bone mineral density T-score | 20.8 (SD 4.5) vs 6.5 (SD 1.1) nmol/L (p=0.001)  -0.73 (SD 0.13) vs -1.61 (SD 0.23) (p=0.006) | NR |
| 16 controls | 61.4 (SD 2.5) |
| Blick (2012) | Prospective observational | 2008 | Men with opioid induced hypogonadism | 90 | 48.3 (SD 12.0, range 20-72) | 90 | Testosterone gel (Testim) | 12 months vs baseline  Serum testosterone  BMFSI score | No significant difference  34.9 vs 27.7 (p<0.001) | 12 months |
| Aloisi (2011a) | Prospective observational | NR | Hypogonadal male chronic non-cancer pain patients on intrathecal morphine | 9 | 59.0 (4.4) range 38-74 | 9 | Testosterone gel | 12 months vs baseline  Serum testosterone  (ref 3.5-8.5)  AMS  SF-36 | 2.99 (SD 0.47) vs 1.16 (SD 0.28) ng/mL p<0.01  Better scores on sexual domain  Better scores on mental domain | 12 months |

NR: not reported, IQR: interquartile range, SEM: standard error of the mean, CI: confidence interval, RCT: randomized controlled trial, IIEF: international index of erectile dysfunction, ADAM: androgen deficiency in ageing males, ISI: insomnia severity index, PCS: pain catastrophizing scale, BMFSI: brief male sexual function inventory, AMS: ageing males’ symptoms scale, SF-36: short form-36

# **Table S7. Risk of bias assessment of the included studies**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study author, year | Consecutive inclusion | Timing and mode of pituitary assessment | Risk of confounding | Total risk of bias |
|
| Singh, 2018 | High | NR | Low | High |
| Yee, 2018 | NR | Low | Low | Low |
| Lehtihet, 2018 | High | NR | Low | High |
| Raheem, 2017 | Low | NR | Low | High |
| Rubinstein, 2017 | Low | High | Low | High |
| Peeters, 2017 | Low | Low | Moderate | Low |
| Huang, 2017 | High | NR | Low | High |
| Reece, 2016 | High | NR | Moderate | High |
| Gibb, 2016 | High | Low | Low | Low |
| Merdin, 2016 | NR | Moderate | NA | Moderate |
| Yang, 2016 | NR | Low | High | Moderate |
| Gerra, 2016 | NR | NR | High | High |
| Kershaw, 2015 | NR | Low | Low | Low |
| Nenke, 2015 | NR | Low | Low | Low |
| Basaria, 2015 | NR | NR | Low | High |
| Valverde-Filho, 2015 | NR | Low | Low | Low |
| Finch, 2015 | NR | Low | Low | Low |
| Rubinstein, 2014 | Low | High | Moderate | High |
| Kim, 2014 | Low | High | NA | High |
| Duarte, 2013 | Low | Low | NA | Low |
| Deyo, 2013 | Low | High | High | High |
| Sunchatawirul, 2012 | NR | Low | Moderate | Moderate |
| Monroe, 2012 | High | NR | Moderate | High |
| Hosseini, 2012 | Low | Low | Low | Low |
| Blick, 2012 | High | High | Moderate | High |
| Gerber, 2012 | High | Low | Low | Low |
| Wong, 2011 | High | Low | NA | Moderate |
| Aurilio, 2011 | High | High | NA | High |
| Aloisi, 2011a | High | NR | Low | High |
| Aloisi, 2011b | High | Low | Low | Low |
| Skipworth, 2011 | Low | Low | Low | Low |
| Rhodin, 2010 | High | Low | Low | Low |
| Fraser, 2009 | High | Low | NA | Low |
| Hallinan, 2009 | Low | NR | Low | Moderate |
| Zhang, 2008 | NR | NR | Low | High |
| Daniell, 2006 | Low | High | Low | Moderate |
| Shahramian, 2006 | NR | High | High | High |
| Bliesener, 2005 | NR | Low | High | Moderate |
| Rajagopal, 2004 | High | High | Low | High |
| Schluger, 2003 | NR | Low | High | Moderate |
| Tennant, 2002 | Low | Low | Low | Low |
| Daniell, 2002 | High | High | NA | High |
| Roberts, 2002 | Low | High | NA | High |
| Stine, 2002 | High | Low | High | Moderate |
| Schluger, 2001 | High | Low | High | Moderate |
| Abs, 2000 | NR | Low | Low | Low |
| Auernhammer, 1994 | High | Low | Low | Low |
| Garland, 1989 | High | Low | Low | Low |
| Ambrosi, 1986 | High | Low | Low | Low |
| Devilla, 1985 | NR | Low | Low | Low |
| Shenkman, 1972 | NR | Low | NA | Low |
| Cushman, 1970 | NR | Low | Low | Low |

NR: not reported, NA: not applicable

# **Supplemental document 1: Search strategy**

**PubMed**

(("Analgesics, Opioid"[mesh] OR "Analgesics, Opioid"[Pharmacological Action] OR "Opiate Alkaloids"[mesh] OR "Opioid Peptides"[mesh] OR "opium"[mesh] OR "opium"[tw] OR "opioid"[tw] OR "Opiate Substitution Treatment"[mesh] OR "Fentanyl"[mesh] OR "Papaverine"[tw] OR "Noscapine"[tw] OR "Naloxone"[tw] OR "Naltrexone"[tw] OR "Buprenorphine"[tw] OR "Nalorphine"[tw] OR "Nalbuphine"[tw] OR "Morphine"[tw] OR "Codeine"[tw] OR "Hydrocodone"[tw] OR "Oxycodone"[tw] OR "Dihydromorphine"[tw] OR "Ethylmorphine"[tw] OR "Heroin"[tw] OR "Hydromorphone"[tw] OR "Oxymorphone"[tw] OR "Thebaine"[tw] OR "Levorphanol"[tw] OR "Levallorphan"[tw] OR "Etorphine"[tw] OR "Diprenorphine"[tw] OR "Dextrorphan"[tw] OR "Dextromethorphan"[tw] OR "Butorphanol"[tw] OR "Buprenorphine"[tw] OR "Benzomorphans"[tw] OR "Pentazocine"[tw] OR "Phenazocine"[tw] OR "nicomorphine"[tw] OR "pethidine"[tw] OR "piritramide"[tw] OR "remifentanil"[tw] OR "sulfentanil"[tw] OR "tapentadol"[tw] OR "tramadol"[tw] OR "alfenta"[tw] OR "butrans"[tw] OR "temgesic"[tw] OR "transtec"[tw] OR "durogesic"[tw] OR "ionsys"[tw] OR "abstral"[tw] OR "Actiq" [tw] OR "breakyl"[tw] OR "effentora"[tw] OR "Instanyl"[tw] OR "pecfent"[tw] OR "palladon"[tw] OR "Oramorph"[tw] OR "MS Contin"[tw] OR " Oxycontin"[tw] OR "oxynorm"[tw] OR "Targinact"[tw] OR "dipidolor"[tw] OR "Sufenta"[tw] OR "Zalviso"[tw] OR "palexia"[tw] OR "tramal"[tw] OR "18,19-dihydroetorphine"[tw] OR "acetaminophen, hydrocodone drug combination"[tw] OR "Alfentanil"[tw] OR "Alphaprodine"[tw] OR "beta-casomorphins"[tw] OR "carfentanil"[tw] OR "deltorphin I, Ala(2)-"[tw] OR "dermorphin"[tw] OR "desomorphine"[tw] OR "Dextromoramide"[tw] OR "Dextropropoxyphene"[tw] OR "dezocine"[tw] OR "dihydrocodeine"[tw] OR "Diphenoxylate"[tw] OR "dynorphin (1-13)"[tw] OR "endomorphin 1"[tw] OR "endomorphin 2"[tw] OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-"[tw] OR "Enkephalin, D-Penicillamine (2,5)-"[tw] OR "enkephalin-Met, Ala(2)-"[tw] OR "eseroline"[tw] OR "Ethylketocyclazocine"[tw] OR "ketobemidone"[tw] OR "lofentanil"[tw] OR "Meperidine"[tw] OR "Meptazinol"[tw] OR "Methadone"[tw] OR "Methadyl Acetate"[tw] OR "nocistatin"[tw] OR "normethadone"[tw] OR "O-demethyltramadol"[tw] OR "paracymethadol"[tw] OR "Phenoperidine"[tw] OR "Pirinitramide"[tw] OR "Promedol"[tw] OR "protopine"[tw] OR "Sufentanil"[tw] OR "Tilidine"[tw] OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine"[tw]) AND ("Hypogonadism"[mesh] OR "Hypogonadism"[tw] OR "hypogonadotropic hypogonadism"[tw] OR "central hypogonadism"[tw] OR "secondary hypogonadism"[tw] OR "hypothalamic-pituitary-gonadal"[tw] OR "HPG"[tw] OR "Adrenal Insufficiency"[mesh] OR "Adrenal Insufficiency"[tw] OR "cortisol deficiency"[tw] OR "secondary adrenal insufficiency"[tw] OR "hypothalamic-pituitary-adrenal"[tw] OR "HPA"[tw] OR "Growth Hormone/deficiency"[Mesh] OR "Growth hormone deficiency"[tw] OR "GH deficiency"[tw] OR "GH-deficiency"[tw] OR "secondary growth hormone deficiency"[tw] OR "secondary GH-deficiency"[tw] OR "hypothalamic-pituitary-growth"[tw] OR "Hypothyroidism"[Mesh] OR "hypothyroidism"[tw] OR "secondary hypothyroidism"[tw] OR "hypothalamic-pituitary-thyroid"[tw] OR "HPT"[tw] OR "prolactin deficiency"[tw] OR "Prolactin/deficiency"[Mesh] OR "Prolactin Deficiency, Isolated"[Supplementary Concept]OR "hypoprolactinemia"[tw] OR "hypoprolactinaemia"[tw] OR hypoprolactinem\*[tw] OR hypoprolactinaem\*[tw] OR "hypothalamic-pituitary-prolactin"[tw]) NOT ("Animals"[mesh] NOT "Humans"[mesh]))

**Embase**

((exp \*"Opiate Agonist"/ OR exp \*"opiate receptor affecting agent"/ OR "opium".ti,ab OR "opioid".ti,ab OR \*"Opiate Substitution Treatment"/ OR \*"Fentanyl"/ OR "Papaverine".ti,ab OR "Noscapine".ti,ab OR "Naloxone".ti,ab OR "Naltrexone".ti,ab OR "Buprenorphine".ti,ab OR "Nalorphine".ti,ab OR "Nalbuphine".ti,ab OR "Morphine".ti,ab OR "Codeine".ti,ab OR "Hydrocodone".ti,ab OR "Oxycodone".ti,ab OR "Dihydromorphine".ti,ab OR "Ethylmorphine".ti,ab OR "Heroin".ti,ab OR "Hydromorphone".ti,ab OR "Oxymorphone".ti,ab OR "Thebaine".ti,ab OR "Levorphanol".ti,ab OR "Levallorphan".ti,ab OR "Etorphine".ti,ab OR "Diprenorphine".ti,ab OR "Dextrorphan".ti,ab OR "Dextromethorphan".ti,ab OR "Butorphanol".ti,ab OR "Buprenorphine".ti,ab OR "Benzomorphans".ti,ab OR "Pentazocine".ti,ab OR "Phenazocine".ti,ab OR "nicomorphine".ti,ab OR "pethidine".ti,ab OR "piritramide".ti,ab OR "remifentanil".ti,ab OR "sulfentanil".ti,ab OR "tapentadol".ti,ab OR "tramadol".ti,ab OR "alfenta".ti,ab OR "butrans".ti,ab OR "temgesic".ti,ab OR "transtec".ti,ab OR "durogesic".ti,ab OR "ionsys".ti,ab OR "abstral".ti,ab OR "Actiq" .ti,ab OR "breakyl".ti,ab OR "effentora".ti,ab OR "Instanyl".ti,ab OR "pecfent".ti,ab OR "palladon".ti,ab OR "Oramorph".ti,ab OR "MS Contin".ti,ab OR " Oxycontin".ti,ab OR "oxynorm".ti,ab OR "Targinact".ti,ab OR "dipidolor".ti,ab OR "Sufenta".ti,ab OR "Zalviso".ti,ab OR "palexia".ti,ab OR "tramal".ti,ab OR "18,19-dihydroetorphine".ti,ab OR "acetaminophen, hydrocodone drug combination".ti,ab OR "Alfentanil".ti,ab OR "Alphaprodine".ti,ab OR "beta-casomorphins".ti,ab OR "carfentanil".ti,ab OR "deltorphin I, Ala(2)-".ti,ab OR "dermorphin".ti,ab OR "desomorphine".ti,ab OR "Dextromoramide".ti,ab OR "Dextropropoxyphene".ti,ab OR "dezocine".ti,ab OR "dihydrocodeine".ti,ab OR "Diphenoxylate".ti,ab OR "dynorphin (1-13)".ti,ab OR "endomorphin 1".ti,ab OR "endomorphin 2".ti,ab OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-".ti,ab OR "Enkephalin, D-Penicillamine (2,5)-".ti,ab OR "enkephalin-Met, Ala(2)-".ti,ab OR "eseroline".ti,ab OR "Ethylketocyclazocine".ti,ab OR "ketobemidone".ti,ab OR "lofentanil".ti,ab OR "Meperidine".ti,ab OR "Meptazinol".ti,ab OR "Methadone".ti,ab OR "Methadyl Acetate".ti,ab OR "nocistatin".ti,ab OR "normethadone".ti,ab OR "O-demethyltramadol".ti,ab OR "paracymethadol".ti,ab OR "Phenoperidine".ti,ab OR "Pirinitramide".ti,ab OR "Promedol".ti,ab OR "protopine".ti,ab OR "Sufentanil".ti,ab OR "Tilidine".ti,ab OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine".ti,ab) AND (\*"Hypogonadism"/ OR "Hypogonadism".ti,ab OR \*"hypergonadotropic hypogonadism"/ OR \*"hypogonadotropic hypogonadism"/ OR "hypogonadotropic hypogonadism".ti,ab OR "central hypogonadism".ti,ab OR "secondary hypogonadism".ti,ab OR "hypothalamic-pituitary-gonadal".ti,ab OR "HPG".ti,ab OR \*"Adrenal Insufficiency"/ OR "Adrenal Insufficiency".ti,ab OR "cortisol deficiency".ti,ab OR "secondary adrenal insufficiency".ti,ab OR "hypothalamic-pituitary-adrenal".ti,ab OR "HPA".ti,ab OR \*"Growth hormone deficiency "/ OR "Growth hormone deficiency".ti,ab OR "GH deficiency".ti,ab OR "GH-deficiency".ti,ab OR "secondary growth hormone deficiency".ti,ab OR "secondary GH-deficiency".ti,ab OR "hypothalamic-pituitary-growth".ti,ab OR exp \*"Hypothyroidism"/ OR "hypothyroidism".ti,ab OR "secondary hypothyroidism".ti,ab OR "hypothalamic-pituitary-thyroid".ti,ab OR "HPT".ti,ab OR "prolactin deficiency".ti,ab OR "hypoprolactinemia".ti,ab OR "hypoprolactinaemia".ti,ab OR "hypothalamic-pituitary-prolactin".ti,ab) AND exp "Humans"/)

**Web of Science**

**(**(TS=("Opiate Agonist" OR "opiate receptor affecting agent" OR "opium" OR "opioid" OR "Opiate Substitution Treatment" OR "Fentanyl" OR "Papaverine" OR "Noscapine" OR "Naloxone" OR "Naltrexone" OR "Buprenorphine" OR "Nalorphine" OR "Nalbuphine" OR "Morphine" OR "Codeine" OR "Hydrocodone" OR "Oxycodone" OR "Dihydromorphine" OR "Ethylmorphine" OR "Heroin" OR "Hydromorphone" OR "Oxymorphone" OR "Thebaine" OR "Levorphanol" OR "Levallorphan" OR "Etorphine" OR "Diprenorphine" OR "Dextrorphan" OR "Dextromethorphan" OR "Butorphanol" OR "Buprenorphine" OR "Benzomorphans" OR "Pentazocine" OR "Phenazocine" OR "nicomorphine" OR "pethidine" OR "piritramide" OR "remifentanil" OR "sulfentanil" OR "tapentadol" OR "tramadol" OR "alfenta" OR "butrans" OR "temgesic" OR "transtec" OR "durogesic" OR "ionsys" OR "abstral" OR "Actiq" OR "breakyl" OR "effentora" OR "Instanyl" OR "pecfent" OR "palladon" OR "Oramorph" OR "MS Contin" OR " Oxycontin" OR "oxynorm" OR "Targinact" OR "dipidolor" OR "Sufenta" OR "Zalviso" OR "palexia" OR "tramal" OR "18,19-dihydroetorphine" OR "acetaminophen, hydrocodone drug combination" OR "Alfentanil" OR "Alphaprodine" OR "beta-casomorphins" OR "carfentanil" OR "deltorphin I, Ala(2)-" OR "dermorphin" OR "desomorphine" OR "Dextromoramide" OR "Dextropropoxyphene" OR "dezocine" OR "dihydrocodeine" OR "Diphenoxylate" OR "dynorphin (1-13)" OR "endomorphin 1" OR "endomorphin 2" OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-" OR "Enkephalin, D-Penicillamine (2,5)-" OR "enkephalin-Met, Ala(2)-" OR "eseroline" OR "Ethylketocyclazocine" OR "ketobemidone" OR "lofentanil" OR "Meperidine" OR "Meptazinol" OR "Methadone" OR "Methadyl Acetate" OR "nocistatin" OR "normethadone" OR "O-demethyltramadol" OR "paracymethadol" OR "Phenoperidine" OR "Pirinitramide" OR "Promedol" OR "protopine" OR "Sufentanil" OR "Tilidine" OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine") AND TI=("Hypogonadism" OR "Hypogonadism" OR "hypergonadotropic hypogonadism" OR "hypogonadotropic hypogonadism" OR "hypogonadotropic hypogonadism" OR "central hypogonadism" OR "secondary hypogonadism" OR "hypothalamic-pituitary-gonadal" OR "HPG" OR "Adrenal Insufficiency" OR "Adrenal Insufficiency" OR "cortisol deficiency" OR "secondary adrenal insufficiency" OR "hypothalamic-pituitary-adrenal" OR "HPA" OR "Growth hormone deficiency " OR "Growth hormone deficiency" OR "GH deficiency" OR "GH-deficiency" OR "secondary growth hormone deficiency" OR "secondary GH-deficiency" OR "hypothalamic-pituitary-growth" OR "Hypothyroidism" OR "hypothyroidism" OR "secondary hypothyroidism" OR "hypothalamic-pituitary-thyroid" OR "HPT" OR "prolactin deficiency" OR "hypoprolactinemia" OR "hypoprolactinaemia" OR "hypothalamic-pituitary-prolactin")) **OR** (TI=("Opiate Agonist" OR "opiate receptor affecting agent" OR "opium" OR "opioid" OR "Opiate Substitution Treatment" OR "Fentanyl" OR "Papaverine" OR "Noscapine" OR "Naloxone" OR "Naltrexone" OR "Buprenorphine" OR "Nalorphine" OR "Nalbuphine" OR "Morphine" OR "Codeine" OR "Hydrocodone" OR "Oxycodone" OR "Dihydromorphine" OR "Ethylmorphine" OR "Heroin" OR "Hydromorphone" OR "Oxymorphone" OR "Thebaine" OR "Levorphanol" OR "Levallorphan" OR "Etorphine" OR "Diprenorphine" OR "Dextrorphan" OR "Dextromethorphan" OR "Butorphanol" OR "Buprenorphine" OR "Benzomorphans" OR "Pentazocine" OR "Phenazocine" OR "nicomorphine" OR "pethidine" OR "piritramide" OR "remifentanil" OR "sulfentanil" OR "tapentadol" OR "tramadol" OR "alfenta" OR "butrans" OR "temgesic" OR "transtec" OR "durogesic" OR "ionsys" OR "abstral" OR "Actiq" OR "breakyl" OR "effentora" OR "Instanyl" OR "pecfent" OR "palladon" OR "Oramorph" OR "MS Contin" OR " Oxycontin" OR "oxynorm" OR "Targinact" OR "dipidolor" OR "Sufenta" OR "Zalviso" OR "palexia" OR "tramal" OR "18,19-dihydroetorphine" OR "acetaminophen, hydrocodone drug combination" OR "Alfentanil" OR "Alphaprodine" OR "beta-casomorphins" OR "carfentanil" OR "deltorphin I, Ala(2)-" OR "dermorphin" OR 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deficiency" OR "secondary adrenal insufficiency" OR "hypothalamic-pituitary-adrenal" OR "HPA" OR "Growth hormone deficiency " OR "Growth hormone deficiency" OR "GH deficiency" OR "GH-deficiency" OR "secondary growth hormone deficiency" OR "secondary GH-deficiency" OR "hypothalamic-pituitary-growth" OR "Hypothyroidism" OR "hypothyroidism" OR "secondary hypothyroidism" OR "hypothalamic-pituitary-thyroid" OR "HPT" OR "prolactin deficiency" OR "hypoprolactinemia" OR "hypoprolactinaemia" OR "hypothalamic-pituitary-prolactin"))**)** NOT ti=(veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR pig OR pigs OR porcine OR horse\* OR equine OR cow OR cows OR bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats)

**Cochrane**

(("Opiate Agonist" OR "opiate receptor affecting agent" OR "opium" OR "opioid" OR "Opiate Substitution Treatment" OR "Fentanyl" OR "Papaverine" OR "Noscapine" OR "Naloxone" OR "Naltrexone" OR "Buprenorphine" OR "Nalorphine" OR "Nalbuphine" OR "Morphine" OR "Codeine" OR "Hydrocodone" OR "Oxycodone" OR "Dihydromorphine" OR "Ethylmorphine" OR "Heroin" OR "Hydromorphone" OR "Oxymorphone" OR "Thebaine" OR "Levorphanol" OR "Levallorphan" OR "Etorphine" OR "Diprenorphine" OR "Dextrorphan" OR "Dextromethorphan" OR "Butorphanol" OR "Buprenorphine" OR "Benzomorphans" OR "Pentazocine" OR "Phenazocine" OR "nicomorphine" OR "pethidine" OR "piritramide" OR "remifentanil" OR "sulfentanil" OR "tapentadol" OR "tramadol" OR "alfenta" OR "butrans" OR "temgesic" OR "transtec" OR "durogesic" OR "ionsys" OR "abstral" OR "Actiq" OR "breakyl" OR "effentora" OR "Instanyl" OR "pecfent" OR "palladon" OR "Oramorph" OR "MS Contin" OR " Oxycontin" OR "oxynorm" OR "Targinact" OR "dipidolor" OR "Sufenta" OR "Zalviso" OR "palexia" OR "tramal" OR "18,19-dihydroetorphine" OR "acetaminophen, hydrocodone drug combination" OR "Alfentanil" OR "Alphaprodine" OR "beta-casomorphins" OR "carfentanil" OR "deltorphin I, Ala(2)-" OR "dermorphin" OR "desomorphine" OR "Dextromoramide" OR "Dextropropoxyphene" OR "dezocine" OR "dihydrocodeine" OR "Diphenoxylate" OR "dynorphin (1-13)" OR "endomorphin 1" OR "endomorphin 2" OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-" OR "Enkephalin, D-Penicillamine (2,5)-" OR "enkephalin-Met, Ala(2)-" OR "eseroline" OR "Ethylketocyclazocine" OR "ketobemidone" OR "lofentanil" OR "Meperidine" OR "Meptazinol" OR "Methadone" OR "Methadyl Acetate" OR "nocistatin" OR "normethadone" OR "O-demethyltramadol" OR "paracymethadol" OR "Phenoperidine" OR "Pirinitramide" OR "Promedol" OR "protopine" OR "Sufentanil" OR "Tilidine" OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine") AND ("Hypogonadism" OR "Hypogonadism" OR "hypergonadotropic hypogonadism" OR "hypogonadotropic hypogonadism" OR "hypogonadotropic hypogonadism" OR "central hypogonadism" OR "secondary hypogonadism" OR "hypothalamic-pituitary-gonadal" OR "HPG" OR "Adrenal Insufficiency" OR "Adrenal Insufficiency" OR "cortisol deficiency" OR "secondary adrenal insufficiency" OR "hypothalamic-pituitary-adrenal" OR "HPA" OR "Growth hormone deficiency " OR "Growth hormone deficiency" OR "GH deficiency" OR "GH-deficiency" OR "secondary growth hormone deficiency" OR "secondary GH-deficiency" OR "hypothalamic-pituitary-growth" OR "Hypothyroidism" OR "hypothyroidism" OR "secondary hypothyroidism" OR "hypothalamic-pituitary-thyroid" OR "HPT" OR "prolactin deficiency" OR "hypoprolactinemia" OR "hypoprolactinaemia" OR "hypothalamic-pituitary-prolactin")):ti,ab,kw

**Emcare**

((exp \*"Opiate Agonist"/ OR exp \*"opiate receptor affecting agent"/ OR "opium".ti,ab OR "opioid".ti,ab OR \*"Opiate Substitution Treatment"/ OR \*"Fentanyl"/ OR "Papaverine".ti,ab OR "Noscapine".ti,ab OR "Naloxone".ti,ab OR "Naltrexone".ti,ab OR "Buprenorphine".ti,ab OR "Nalorphine".ti,ab OR "Nalbuphine".ti,ab OR "Morphine".ti,ab OR "Codeine".ti,ab OR "Hydrocodone".ti,ab OR "Oxycodone".ti,ab OR "Dihydromorphine".ti,ab OR "Ethylmorphine".ti,ab OR "Heroin".ti,ab OR "Hydromorphone".ti,ab OR "Oxymorphone".ti,ab OR "Thebaine".ti,ab OR "Levorphanol".ti,ab OR "Levallorphan".ti,ab OR "Etorphine".ti,ab OR "Diprenorphine".ti,ab OR "Dextrorphan".ti,ab OR "Dextromethorphan".ti,ab OR "Butorphanol".ti,ab OR "Buprenorphine".ti,ab OR "Benzomorphans".ti,ab OR "Pentazocine".ti,ab OR "Phenazocine".ti,ab OR "nicomorphine".ti,ab OR "pethidine".ti,ab OR "piritramide".ti,ab OR "remifentanil".ti,ab OR "sulfentanil".ti,ab OR "tapentadol".ti,ab OR "tramadol".ti,ab OR "alfenta".ti,ab OR "butrans".ti,ab OR "temgesic".ti,ab OR "transtec".ti,ab OR "durogesic".ti,ab OR "ionsys".ti,ab OR "abstral".ti,ab OR "Actiq" .ti,ab OR "breakyl".ti,ab OR "effentora".ti,ab OR "Instanyl".ti,ab OR "pecfent".ti,ab OR "palladon".ti,ab OR "Oramorph".ti,ab OR "MS Contin".ti,ab OR " Oxycontin".ti,ab OR "oxynorm".ti,ab OR "Targinact".ti,ab OR "dipidolor".ti,ab OR "Sufenta".ti,ab OR "Zalviso".ti,ab OR "palexia".ti,ab OR "tramal".ti,ab OR "18,19-dihydroetorphine".ti,ab OR "acetaminophen, hydrocodone drug combination".ti,ab OR "Alfentanil".ti,ab OR "Alphaprodine".ti,ab OR "beta-casomorphins".ti,ab OR "carfentanil".ti,ab OR "deltorphin I, Ala(2)-".ti,ab OR "dermorphin".ti,ab OR "desomorphine".ti,ab OR "Dextromoramide".ti,ab OR "Dextropropoxyphene".ti,ab OR "dezocine".ti,ab OR "dihydrocodeine".ti,ab OR "Diphenoxylate".ti,ab OR "dynorphin (1-13)".ti,ab OR "endomorphin 1".ti,ab OR "endomorphin 2".ti,ab OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-".ti,ab OR "Enkephalin, D-Penicillamine (2,5)-".ti,ab OR "enkephalin-Met, Ala(2)-".ti,ab OR "eseroline".ti,ab OR "Ethylketocyclazocine".ti,ab OR "ketobemidone".ti,ab OR "lofentanil".ti,ab OR "Meperidine".ti,ab OR "Meptazinol".ti,ab OR "Methadone".ti,ab OR "Methadyl Acetate".ti,ab OR "nocistatin".ti,ab OR "normethadone".ti,ab OR "O-demethyltramadol".ti,ab OR "paracymethadol".ti,ab OR "Phenoperidine".ti,ab OR "Pirinitramide".ti,ab OR "Promedol".ti,ab OR "protopine".ti,ab OR "Sufentanil".ti,ab OR "Tilidine".ti,ab OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine".ti,ab) AND (\*"Hypogonadism"/ OR "Hypogonadism".ti,ab OR \*"hypergonadotropic hypogonadism"/ OR \*"hypogonadotropic hypogonadism"/ OR "hypogonadotropic hypogonadism".ti,ab OR "central hypogonadism".ti,ab OR "secondary hypogonadism".ti,ab OR "hypothalamic-pituitary-gonadal".ti,ab OR "HPG".ti,ab OR \*"Adrenal Insufficiency"/ OR "Adrenal Insufficiency".ti,ab OR "cortisol deficiency".ti,ab OR "secondary adrenal insufficiency".ti,ab OR "hypothalamic-pituitary-adrenal".ti,ab OR "HPA".ti,ab OR \*"Growth hormone deficiency "/ OR "Growth hormone deficiency".ti,ab OR "GH deficiency".ti,ab OR "GH-deficiency".ti,ab OR "secondary growth hormone deficiency".ti,ab OR "secondary GH-deficiency".ti,ab OR "hypothalamic-pituitary-growth".ti,ab OR exp \*"Hypothyroidism"/ OR "hypothyroidism".ti,ab OR "secondary hypothyroidism".ti,ab OR "hypothalamic-pituitary-thyroid".ti,ab OR "HPT".ti,ab OR "prolactin deficiency".ti,ab OR "hypoprolactinemia".ti,ab OR "hypoprolactinaemia".ti,ab OR "hypothalamic-pituitary-prolactin".ti,ab) AND exp "Humans"/)

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TI(("Opiate Agonist" OR "opiate receptor affecting agent" OR "opium" OR "opioid" OR "Opiate Substitution Treatment" OR "Fentanyl" OR "Papaverine" OR "Noscapine" OR "Naloxone" OR "Naltrexone" OR "Buprenorphine" OR "Nalorphine" OR "Nalbuphine" OR "Morphine" OR "Codeine" OR "Hydrocodone" OR "Oxycodone" OR "Dihydromorphine" OR "Ethylmorphine" OR "Heroin" OR "Hydromorphone" OR "Oxymorphone" OR "Thebaine" OR "Levorphanol" OR "Levallorphan" OR "Etorphine" OR "Diprenorphine" OR "Dextrorphan" OR "Dextromethorphan" OR "Butorphanol" OR "Buprenorphine" OR "Benzomorphans" OR "Pentazocine" OR "Phenazocine" OR "nicomorphine" OR "pethidine" OR "piritramide" OR "remifentanil" OR "sulfentanil" OR "tapentadol" OR "tramadol" OR "alfenta" OR "butrans" OR "temgesic" OR "transtec" OR "durogesic" OR "ionsys" OR "abstral" OR "Actiq" OR "breakyl" OR "effentora" OR "Instanyl" OR "pecfent" OR "palladon" OR "Oramorph" OR "MS Contin" OR " Oxycontin" OR "oxynorm" OR "Targinact" OR "dipidolor" OR "Sufenta" OR "Zalviso" OR "palexia" OR "tramal" OR "18,19-dihydroetorphine" OR "acetaminophen, hydrocodone drug combination" OR "Alfentanil" OR "Alphaprodine" OR "beta-casomorphins" OR "carfentanil" OR "deltorphin I, Ala(2)-" OR "dermorphin" OR "desomorphine" OR "Dextromoramide" OR "Dextropropoxyphene" OR "dezocine" OR "dihydrocodeine" OR "Diphenoxylate" OR "dynorphin (1-13)" OR "endomorphin 1" OR "endomorphin 2" OR "Enkephalin, Ala(2)-MePhe(4)-Gly(5)-" OR "Enkephalin, D-Penicillamine (2,5)-" OR "enkephalin-Met, Ala(2)-" OR "eseroline" OR "Ethylketocyclazocine" OR "ketobemidone" OR "lofentanil" OR "Meperidine" OR "Meptazinol" OR "Methadone" OR "Methadyl Acetate" OR "nocistatin" OR "normethadone" OR "O-demethyltramadol" OR "paracymethadol" OR "Phenoperidine" OR "Pirinitramide" OR "Promedol" OR "protopine" OR "Sufentanil" OR "Tilidine" OR "tyrosyl-1,2,3,4-tetrahydro-3-isoquinolinecarbonyl-phenylalanyl-phenylalanine") AND ("Hypogonadism" OR "Hypogonadism" OR "hypergonadotropic hypogonadism" OR "hypogonadotropic hypogonadism" OR "hypogonadotropic hypogonadism" OR "central hypogonadism" OR "secondary hypogonadism" OR "hypothalamic-pituitary-gonadal" OR "HPG" OR "Adrenal Insufficiency" OR "Adrenal Insufficiency" OR "cortisol deficiency" OR "secondary adrenal insufficiency" OR "hypothalamic-pituitary-adrenal" OR "HPA" OR "Growth hormone deficiency " OR "Growth hormone deficiency" OR "GH deficiency" OR "GH-deficiency" OR "secondary growth hormone deficiency" OR "secondary GH-deficiency" OR "hypothalamic-pituitary-growth" OR "Hypothyroidism" OR "hypothyroidism" OR "secondary hypothyroidism" OR "hypothalamic-pituitary-thyroid" OR "HPT" OR "prolactin deficiency" OR "hypoprolactinemia" OR "hypoprolactinaemia" OR "hypothalamic-pituitary-prolactin") NOT (veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR pig OR pigs OR porcine OR horse\* OR equine OR cow OR cows OR bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats))

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# **Supplemental document 2: Risk of bias assessment guide**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Low | Moderate | High |
| Consecutive inclusion | Consecutive inclusion of opioid users or random sample of inception cohort |  | Non-consecutive inclusion |
| Hormonal assessment | Dynamic test for HPA- and somatotropic axes, morning values for other axis | Morning values for all hormones, IGF-I for somatotropic axis, no dynamic testing | Random timing, no dynamic testing, GH levels for somatotropic axis |
| Risk of confounding in comparable studies | Opioid users and controls are from the same study population or adequate correction is applied (at minimum for age, sex, comorbidity) | Correction for confounding is mentioned, but factors analyzed are not | Opioid users with pain syndrome or addiction are compared with healthy controls, no correction is applied for confounding factors |

# **Supplemental document 3: List of included articles**

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