Opioids and hypogonadism with ageing

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UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

Opioid therapy and hypogonadism

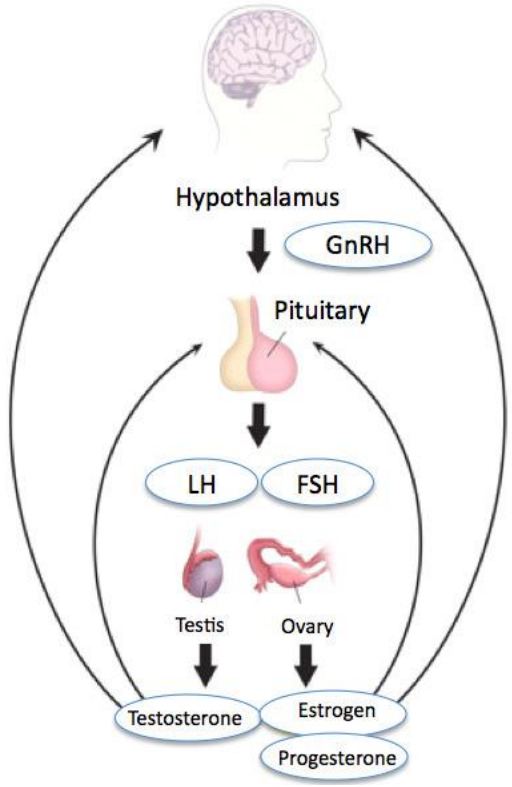
- Opioids known to have negative effects on the endocrine system, particularly that of hypogonadotropic hypogonadism *(little or no hormone produced by the testes or ovaries)*
- For both genders hypogonadism can present in multiple ways with signs or symptoms of:
  - Decreased libido
  - Fatigue
  - Depressed mood
  - Sarcopenia *(loss of muscle due to ageing, chronic illness leading to immobility, general ill health)*
  - Osteoporosis *(loss of bone, leading to increased risk of fractures)*
  - Impotence, oligospermia (men)
  - Infertility, menstrual irregularity (women)

Hypothalamus-pituitary-gonadal axis

- Gonadotropin releasing hormone (GnRH) stimulates > pituitary gland which > produces luteinizing hormone (LH) and follicle stimulating hormone (FSH) > stimulates the gonads (testes/ovaries) to produce sex hormones

- Sex hormones support normal sexual and reproductive function:
  - Testosterone in men
  - Oestrogen + progesterone in women

- The sex hormones subsequently exert negative feedback on hypothalamus and pituitary to control secretion of GnRH, LH and FSH



Opioid receptors throughout the axis

- The hypothalamic-pituitary-gonadal axis is modulated by external influences as well – one such influence is opioids (both endogenous and exogenous)
- Opioids can bind to opioid receptors, primarily in the hypothalamus, to modulate gonadal function
- Have been shown to interfere with normal pulsatility of GnRH resulting in decreased release of LH and FSH
- In addition to effects on hypothalamus, pre-clinical studies have shown evidence of opioid receptors on pituitary gland, testis, ovarian tissue suggesting further down axis suppression
- Shown to alter adrenal production of dehydroepiandrosterone (DHEA) – major precursor to both testosterone (men) and estradiol (women)

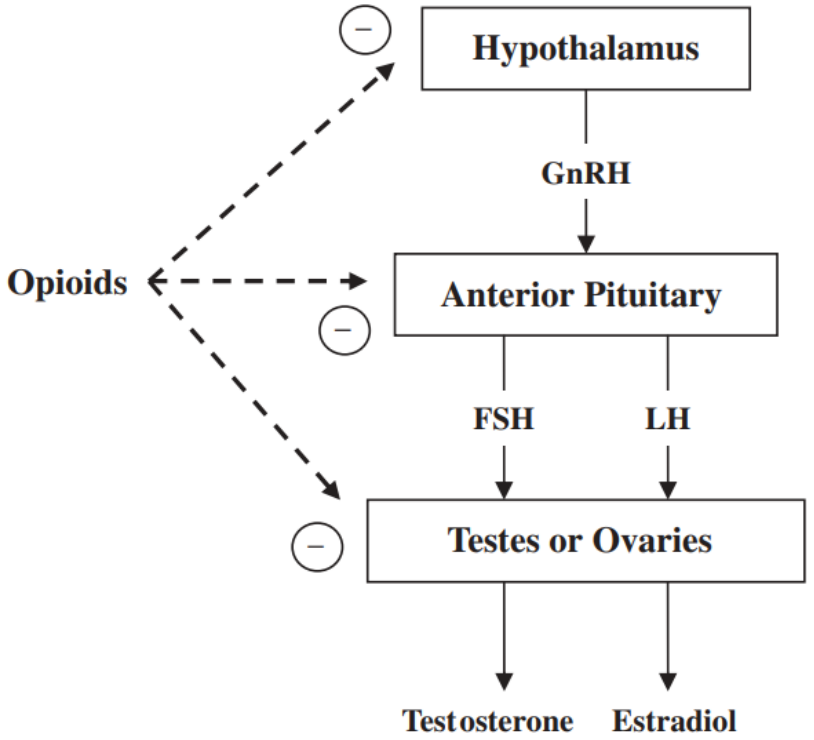


FIGURE 1. Interactions between opioids and the reproductive endocrine system.

[1] https://pubmed.ncbi.nlm.nih.gov/14622741/

Real world opioid therapy (1)

One case control study of patients with chronic pain not due to malignancy revealed:

- 25/29 (86.2%) of patients treated with chronic opioid therapy
- had evidence of **subnormal serum hormones**
- compared with 1/10 (10.0%) of patients with chronic pain not receiving opioid therapy [1]

Real world opioid therapy (2)

Cohort study in men

showed sub-normal testosterone levels in 40/54 (74.1%) in men on long acting oral opioids

(methadone, oxycontin, sustained action oral morphine)

compared with 2/27 (7.4%) men not taking opioids (p<0.0001)

with an associated dose-related pattern [2]

Table 2. Ave hormone levels in men consuming sustained-action opioids in multiple daily doses

Methadone equivalents (daily consumption)	No. of men	Age average (years)	Testosterone	
			Free (pg/mL)	Total* (ng/dL)
0	27	57.4	127.4 (±48.8)	449.1 (±181.1)
20-60 mg	15	51.9	74.3 (±43.5)	265.8 (±191.9)
70-120 mg	23	49.4	41.7 (±25.5)	188.5 (±193.4)
>120 mg	16	47.8	44.8 (±26.3)	172.1 (±108.8)
Normal range			50-210	260-1000

[2] https://pubmed.ncbi.nlm.nih.gov/11014399/
[3] https://pubmed.ncbi.nlm.nih.gov/14622741/

Hypogonadism and bone health

- Hypogonadism associated with osteoporosis in both males and females

- Testosterone has been shown to have **direct effects** on proliferation and differentiation of osteoblasts (*cells that form new bone*) as well as inhibit osteoclast *(cells that break down bone)*

- Testosterone also affects bone through aromatisation to oestrogen *(conversion of testosterone to oestrogen)*

- Oestrogen inhibits osteoclastic bone resorption *(ie. oestrogen lessens bone breakdown)*
  - hence why post-menopausal women (who have low oestrogen) are at increased risk of osteoporosis

Opioids and fractures

Overall relative risk of opioid therapy and fractures shown to be 1.78 (95% CI 1.53-2.07) in meta-analysis of cohort and case control studies of chronic opioid therapy [3].

Underlying reason for this is multi-factorial:

- Osteoporosis (increasing over the life cycle)
- Sarcopenia *(loss of muscle due to ageing, chronic illness leading to immobility, general ill health)*
- Intrinsic risks of opioid therapy itself (sedation, drowsiness, increased risk of delirium) increasing likelihood of bad falls

[4] https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0220216#pone.0220216.ref034

Osteoporosis risk assessment, diagnosis and management

Recommendations restricted to postmenopausal women and men aged >50 years

Royal Australian College *of* General Practitioners

osteoporosis australia

Minimal trauma hip or vertebral fracture

DXA to establish baseline BMD – recommended but not essential

Initiate treatment with anti-osteoporosis medication
- Bisphosphonates (Grade A)
- Denosumab (Grade A women, Grade B men)
- Oestrogen replacement therapy (Grade A)

Address lifestyle risk factors
- Implement falls reduction strategies (Grade A)
- Encourage balance training and resistance exercise (Grade A)
- Modify diet, smoking and alcohol intake (Grade C)
- Provide education and psychosocial support (Grade D)

Minimal trauma fracture at any other site*

DXA of spine and proximal femur (Grade A)

- T-score ≤–1.5 → **Initiate treatment with anti-osteoporosis medication**
  - Bisphosphonates (Grade A)
  - Denosumab (Grade A women, Grade B men)
  - Oestrogen replacement therapy (Grade A)
- T-score >–1.5 → **Consider specialist referral**

Address lifestyle risk factors
- Implement falls reduction strategies (Grade A)
- Encourage balance training and resistance exercise (Grade A)
- Modify diet, smoking and alcohol intake (Grade C)
- Provide education and psychosocial support (Grade D)

No history of minimal trauma fracture

Aged ≥70 years‡ (Grade D Consensus)

Assess risk factor profile (Grade B) Major risk factors that qualify for MBS reimbursement of DXA†

Non-modifiable
- Parental history of fracture

Modifiable and lifestyle
- Premature menopause†
- Hypogonadism†
- Multiple falls
- Low physical activity or immobility
- Low body weight
- Low muscle mass and strength
- Poor balance
- Protein or calcium undernutrition
- Smoking
- Alcohol >2 standard drinks/day
- Vitamin D insufficiency

Diseases or conditions§
- Rheumatoid arthritis†
- Hyperthyroidism†
- Hyperparathyroidism†
- Chronic kidney disease†
- Chronic liver disease†
- Coeliac disease or malabsorption†
- Diabetes mellitus
- Myeloma or MGUS
- Organ transplant
- Bone marrow transplant
- HIV infection
- Depression

Medications (large effect)
- Glucocorticoids†‖ (>3 months≥7.5 mg/day)
- Excess thyroid hormone replacement
- Aromatase inhibitors
- Anti-androgen therapy†

Medications (modest effect)
- SSRIs
- Anti-psychotics
- Thiazolidenediones
- Anti-epileptic medications
- PPIs

DXA of spine and proximal femur (Grade A)

T-score ≤–2.5? → No → **Estimate absolute fracture risk** Garvan Fracture Risk Calculator or FRAX (Grade D Consensus)

- Yes → **High 10-year risk of fracture** Hip fracture >3%, any fracture >20% OR **T-score** ≤–2.5 → **Initiate treatment with anti-osteoporosis medication**
  - Bisphosphonates (Grade A)
  - Denosumab (Grade A women, Grade B men)
  - Oestrogen replacement therapy (Grade A)
- Low risk of fracture → Treatment not recommended

Address lifestyle risk factors
- Implement falls reduction strategies (Grade A)
- Encourage balance training and resistance exercise (Grade A)
- Modify diet, smoking and alcohol intake (Grade C)
- Provide education and psychosocial support (Grade D)

BMD Bone mineral density
DXA Dual energy X-ray absorptiometry
HIV Human immunodeficiency virus
MBS Medicare Benefits Schedule
MGUS Monoclonal gammopathy of undetermined significance
PPIs Proton pump inhibitors
SSRIs Selective serotonin reuptake inhibitor

* Excluding fingers and toes
† Qualifies for MBS reimbursement of BMD testing
‡ Consensus recommendation. The MBS reimburses costs for measurement of BMD testing in any person aged ≥70 years
‖ See other guidelines specific to glucocorticoid treatment for more information and recommendations regarding glucocorticoid use and risk of osteoporosis and fracture
§ Treatment of an underlying condition may improve bone strength

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Treatment considerations (1)

- Opioid dose and duration

- Bone health:
  - Lifestyle measures including diet, weight-bearing exercise
  - DEXA scans
  - Calcium replacement (600-1200mg/d typically depending on dairy intake)
  - Vitamin D3 replacement (at least 800 IU/d)
  - Anti-resorptive therapy (Based on T-score or FRAX score)

- Hormone replacement – discuss pros/cons with the individual

Treatment considerations (2)

- Currently conflicting evidence regarding role for testosterone replacement therapy (TRT) in men given associated risk of metabolic syndrome (hypertension, dyslipidaemia) in the general population

- One study suggests minimal benefit on quality life with no improvement in sleep quality, mood, sexual or physical function [6]

- Another analysis of 21,272 long-term male opioid users indicated TRT had lower all-cause mortality including MACE, anaemia and hip fractures [7]

- Limited evidence for hormone replacement for women with hypogonadism secondary to opioid therapy but similar approach to menopausal hormone therapy is advised with serum hormone levels measured prior to trial of repletion [8]

References

[1] https://pubmed.ncbi.nlm.nih.gov/14622741/
[2] https://pubmed.ncbi.nlm.nih.gov/11014399/
[3] https://pubmed.ncbi.nlm.nih.gov/14622741/
[4] https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0220216#pone.0220216.ref034
[5] https://sydney.edu.au/medicine/cdpc/documents/resources/RACGP%20osteoporosis-guidelines_2017.pdf
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any
questions?