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HEALTH AUSTRALIA

# Endocrinological Effects of Long Term Opioids

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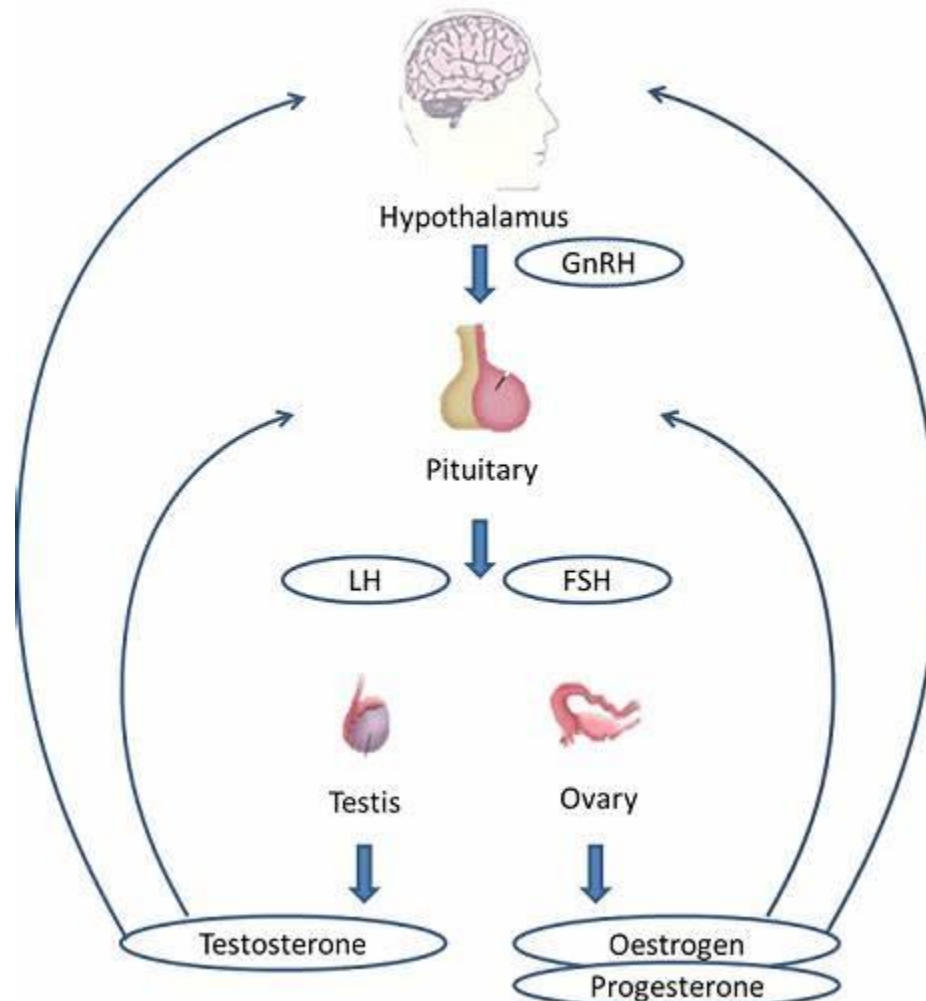
UNDER THE STEWARDSHIP OF MARY AIKENHEAD MINISTRIES

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- **Opioid use impact on hypothalamic-pituitary-gonadal axis well studied - for people on MMT known > 40 years (50-85% of people)**
  - **independent of route**
  - **long acting > short acting**
  - **effects commence with commencement of treatment and HPG axis typically recovers on cessation**
  - **full agonist > partial agonist**

# Hypothalamus-pituitary-gonadal axis



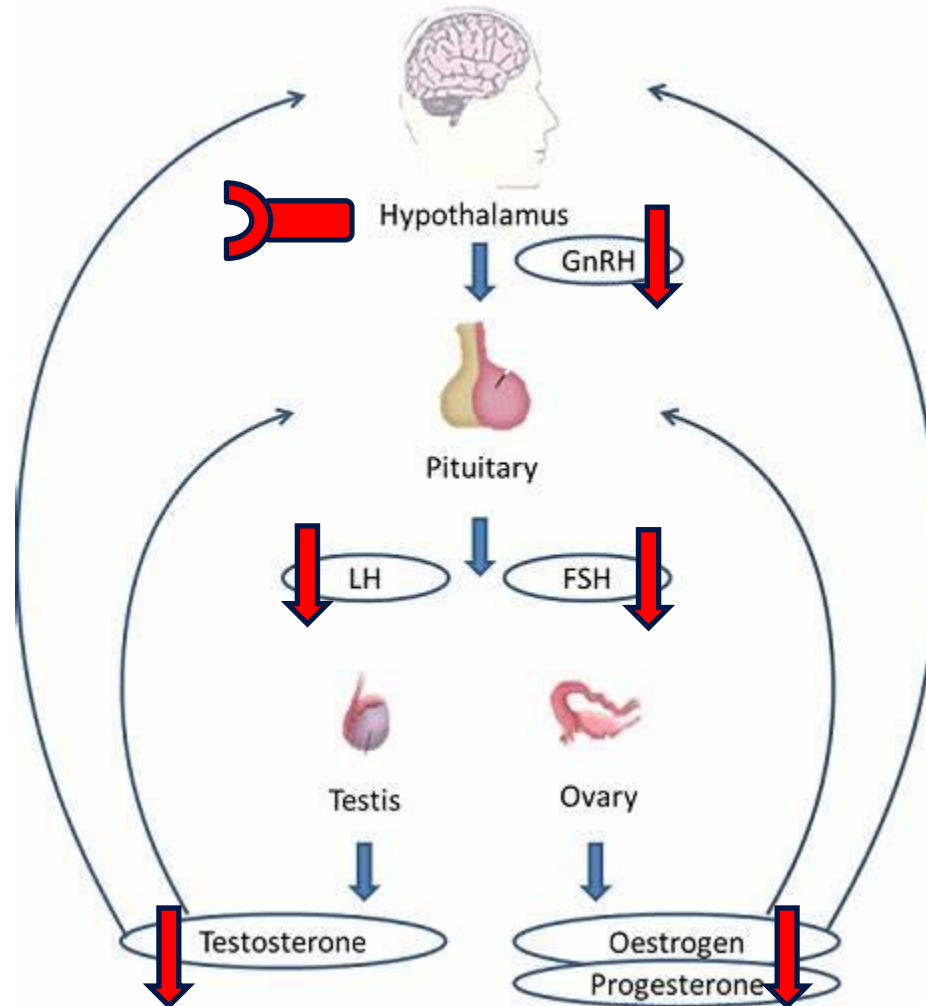
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# Hypothalamus-pituitary-gonadal axis



  
Opioid



# Consequences of hypogonadism

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Mood and cognition

Muscles and bones

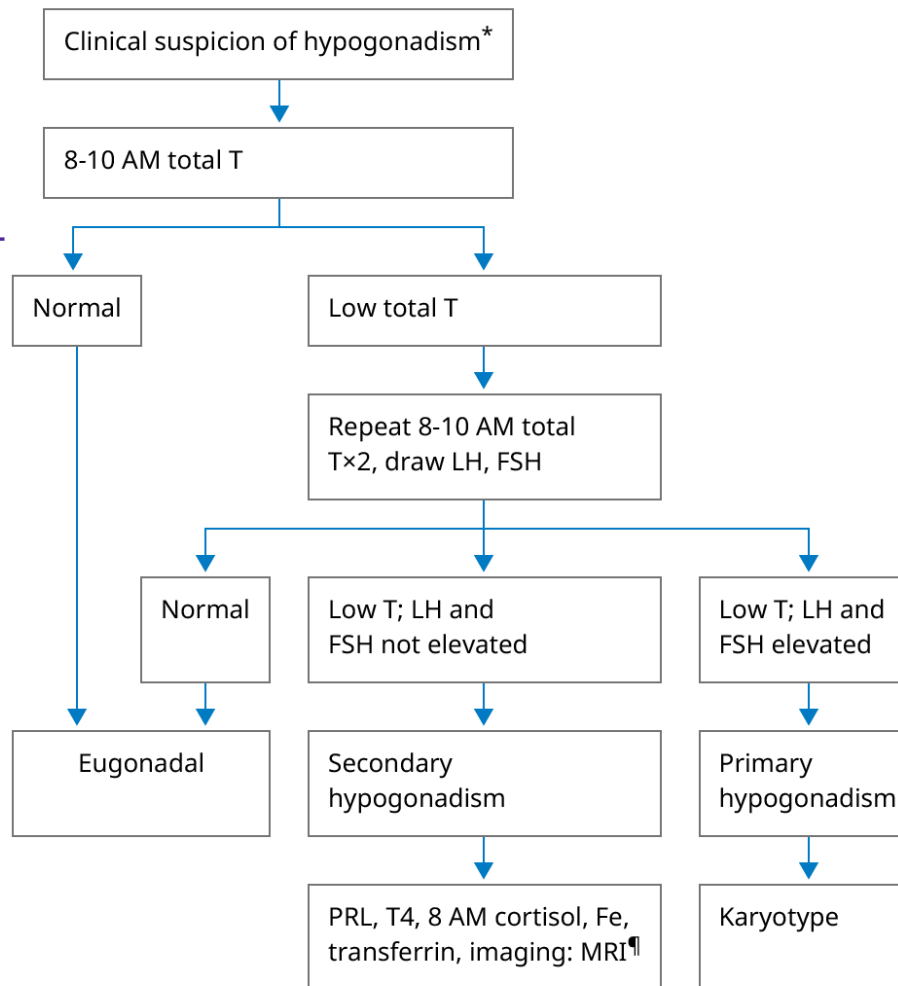
Cardiovascular system

Sexual drive (libido)



- Depressed mood
- Fatigue
- Sarcopenia (loss of muscle)
- Osteoporosis (loss of bone)
- Decreased libido
- Impotence, oligospermia (men)
- Infertility, menstrual irregularity (women)

## Evaluation of the male with possible hypogonadism



Fe: iron; FSH: follicle-stimulating hormone; LH: luteinizing hormone; MRI: magnetic resonance imaging; PRL: prolactin; T: testosterone; T4: thyroxine.

\* This algorithm applies to the evaluation of outpatients. Males with acute or subacute illness should not be assessed for hypogonadism, as they will have a transient functional secondary hypogonadism.

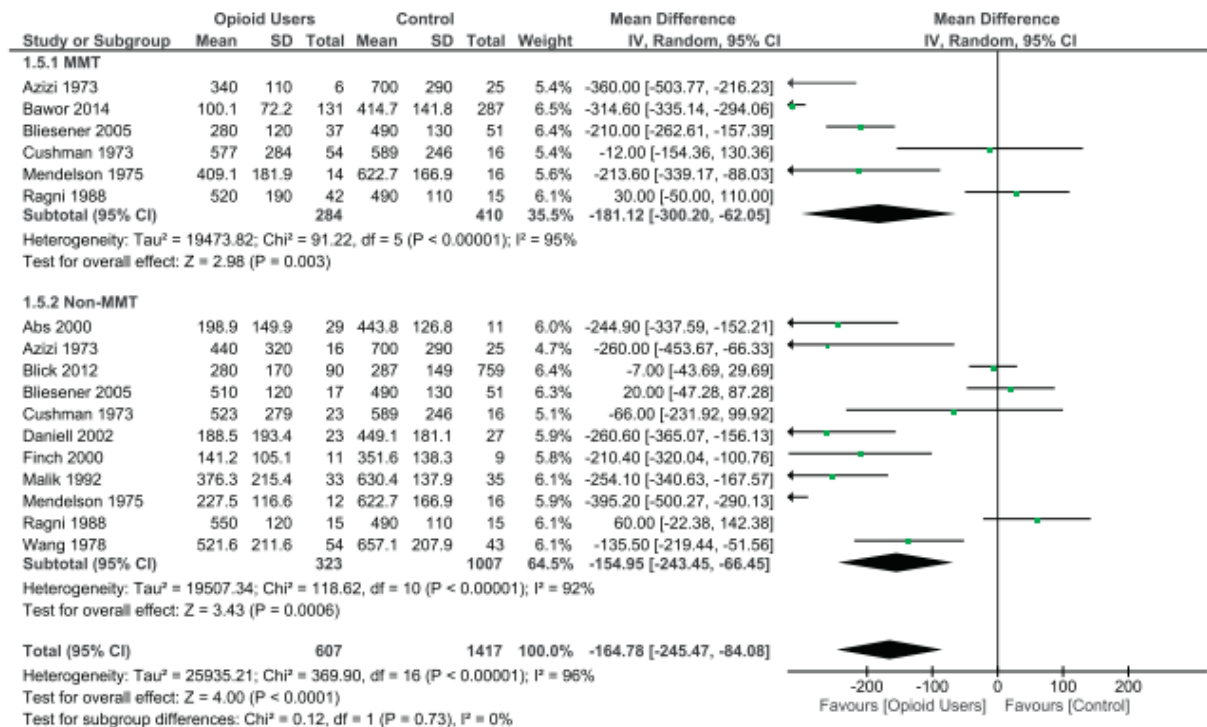
¶ Iron and transferrin are measured to assess the possibility that hemochromatosis is the cause of secondary hypogonadism. When an MRI should be performed depends upon several factors. One is the patient's serum T relative to his age. A male <40 years with a serum T <250 ng/dL (8.7 nmol/L) warrants an MRI, but in a male >60 years, a value of <150 ng/dL (5.2 nmol/L) would be necessary to warrant it. An MRI should also be performed if other pituitary hormones are abnormal, eg, if serum prolactin is elevated or if serum T4 and/or early morning cortisol are below normal.

Adapted from: Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. JCEM 2010; 95:2536.

# Real world opioid therapy (1)

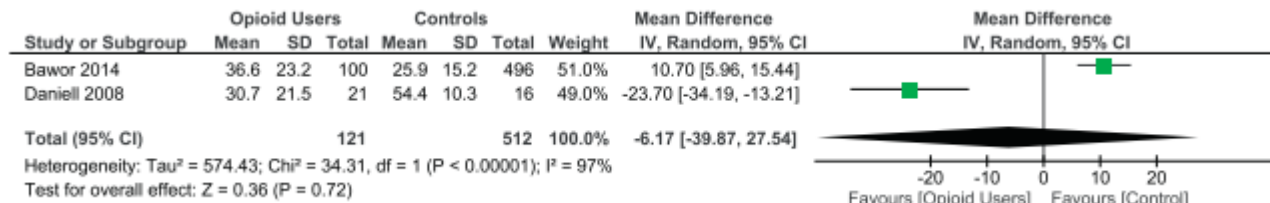
One meta-analysis (n = 2769) of a heterogeneous group of opioid users:

- Significant reduction in mean testosterone level in men (mean difference -164.78,  $p < 0.0001$ )
- Methadone affected testosterone levels similarly to other opioids



# Real world opioid therapy (2)

- No difference in testosterone levels observed in women



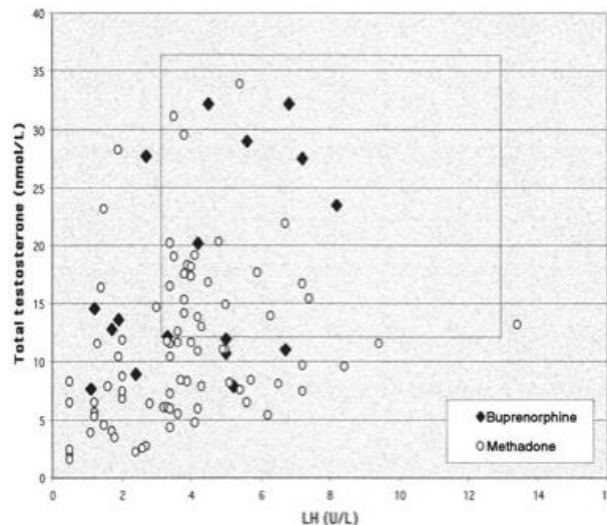


# Real world opioid therapy (2)

## Hypogonadism in men receiving methadone and buprenorphine maintenance treatment

R. Hallinan,\* A. Byrne,\* K. Agho,† C. G. McMahon,‡ P. Tynan§ and J. Attia¶

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**Figure 1** Total testosterone plotted against luteinising hormone (LH) for 17 buprenorphine treated men and 81 methadone treated men. Four men with incomplete data for LH and one outlier are excluded. The square zone represents the normal reference ranges for these hormones (Daniell, 2002a).

- N = 103 men (mean age 37.6)
- 65% Methadone and 28% **buprenorphine** had low testosterone
- 39% Methadone and 11% buprenorphine had testosterone levels <8.0 nM\*

\*Levels that could warrant androgen replacement therapy according to Australian consensus guidelines

## Real world opioid therapy (3)

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### **Increased risk of reproductive dysfunction in women prescribed long-term opioids for musculoskeletal pain: A matched cohort study in the Clinical Practice Research Datalink**

E. Richardson, J. Bedson, Y. Chen, R. Lacey, K.M. Dunn

Large study of women (n = 44,260)

Long-term opioid use ( $\geq 90$  days) for chronic non-cancer pain was associated with:

- Higher risk of oligomenorrhoea and amenorrhoea  
(hazard ratio 1.13, 95% CI 1.05-1.21)
- Higher risk of menopause  
(hazard ratio 1.16, 95% CI 1.10-1.23)

# Hypothalamic-Pituitary-Adrenal Axis

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- **HPA axis – inhibited at hypothalamic level**
- **both acute and chronic effect**
- **reduced response to synthetic ACTH in approx. 15% (though accurate prevalence not well defined)**
- **dose related**
  
- **many case studies of people on long term opioids presenting with adrenal crisis (typically along with another medical illness)**
- **resolves once opioids are weaned**
  
- **implications for routine practice (screening?) are unclear**

# Other

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**Growth Hormone – opioids increase GH secretion acutely but data on long term use inconclusive**

**Prolactin levels – data variable**

**Thyroid – increase TSH with no impact on T3,T4 acutely or chronically**

**ASH/Oxytocin – nil data**

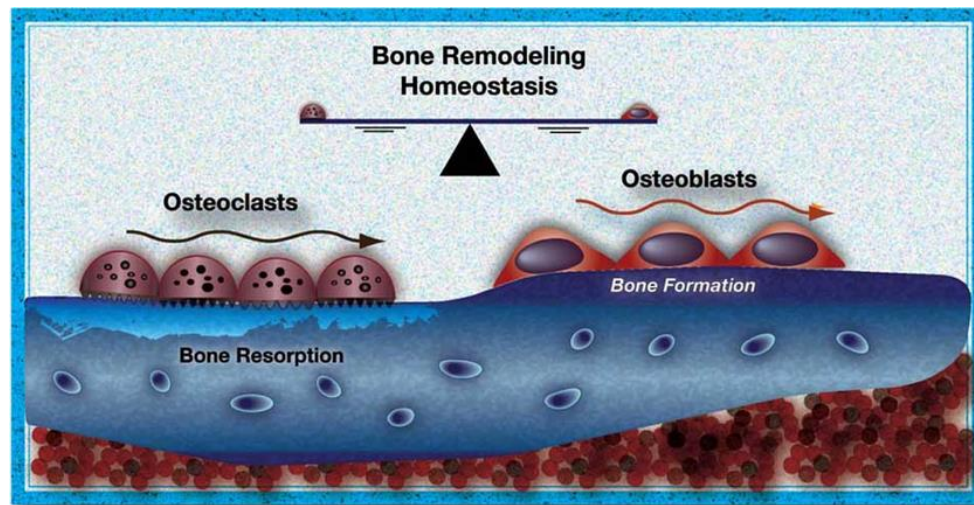
# SKELETAL EFFECTS

# Opioids and bone health

Opioids reduce Bone Mineral Density (BMD) and increase fracture risk (**risk of hip fracture (OR 1.38 - 2.00)**)

3 mechanisms

- Inhibits bone formation by osteoblasts
- Hypogonadism (indirect) > sex hormones prevent bone breakdown by osteoclasts
- High risk of falls (sedation, dizziness)



# Options - summary

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- **Weaning opioids – generally full recovery of HPG axis**
- **Switch to buprenorphine**
- **In ongoing hypogonadism – consider androgen replacement**
- **Screen for Osteoporosis with BMD**
  - **at lower age than typical > 40?**

# Thoughts

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- **relatively common when tested for**
- **symptoms are common but overlap with other comorbid diagnoses**  
**eg. under-treatment with OAT, MDD, obstructive sleep apnoea**
- **little consensus on treatment**
- **systems (outside general practice) lack confidence**
- **as aging cohort osteoporosis screening and management should be prioritised**



# References

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## Opioid Induced Endocrinopathies

Fountas A, Van Uum, S, Karavataki N

Lancet Diabetes and Endocrinology Jan 2020

