Long-term Effects of Opioid Use in Adolescence

Dr Connie Chong

Adolescent and Young Adult Addiction Medicine Fellow9

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Introduction

Long-term effects of opioids have been known for >40 years:

Endocrine

Skeletal

Sleep

Immune

Cardiovascular

Neuropsychiatric

Underdiagnosed due to

- Symptom under-reporting by patients
- Poor awareness among clinicians
- No consensus or clinical guidelines

Introduction

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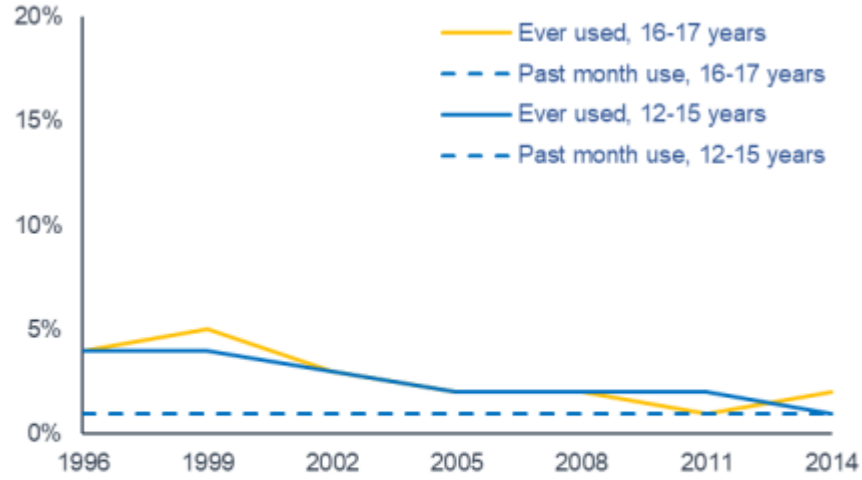
Adolescents and opioids

- Student use of heroin or other opioids remains low (~1%)
- However, dispensing of strong opioids to Australian children and adolescents has increased every year between 2013-2017
- In 2017, one in 25 adolescents were dispensed an opioid
- Paucity of data on this sub-population



Percentage of Australian secondary school students who used opiates, ASSAD 1996-2014

ST VINCENT'S HEALTH AUSTRALIA

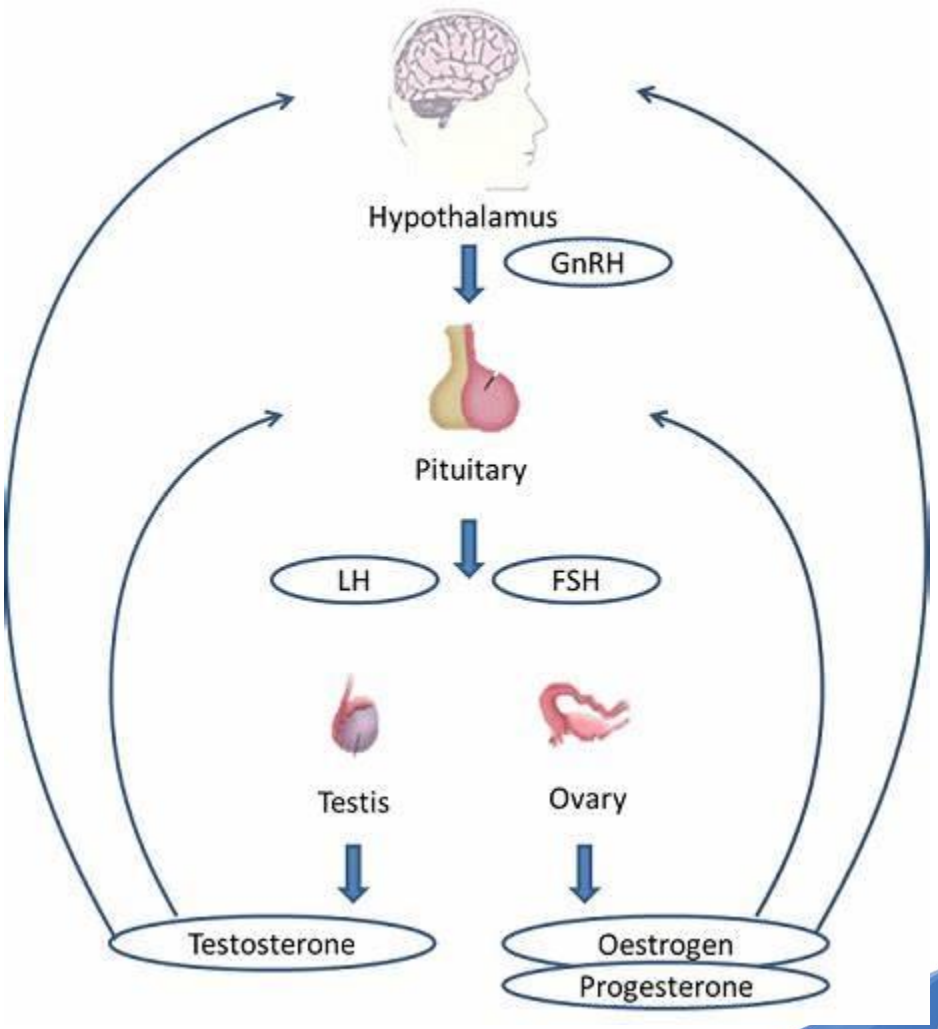
OPIOIDS AND HYPOGONADISM

Opioids and hypogonadism

Hypogonadism = suppression of sex hormones

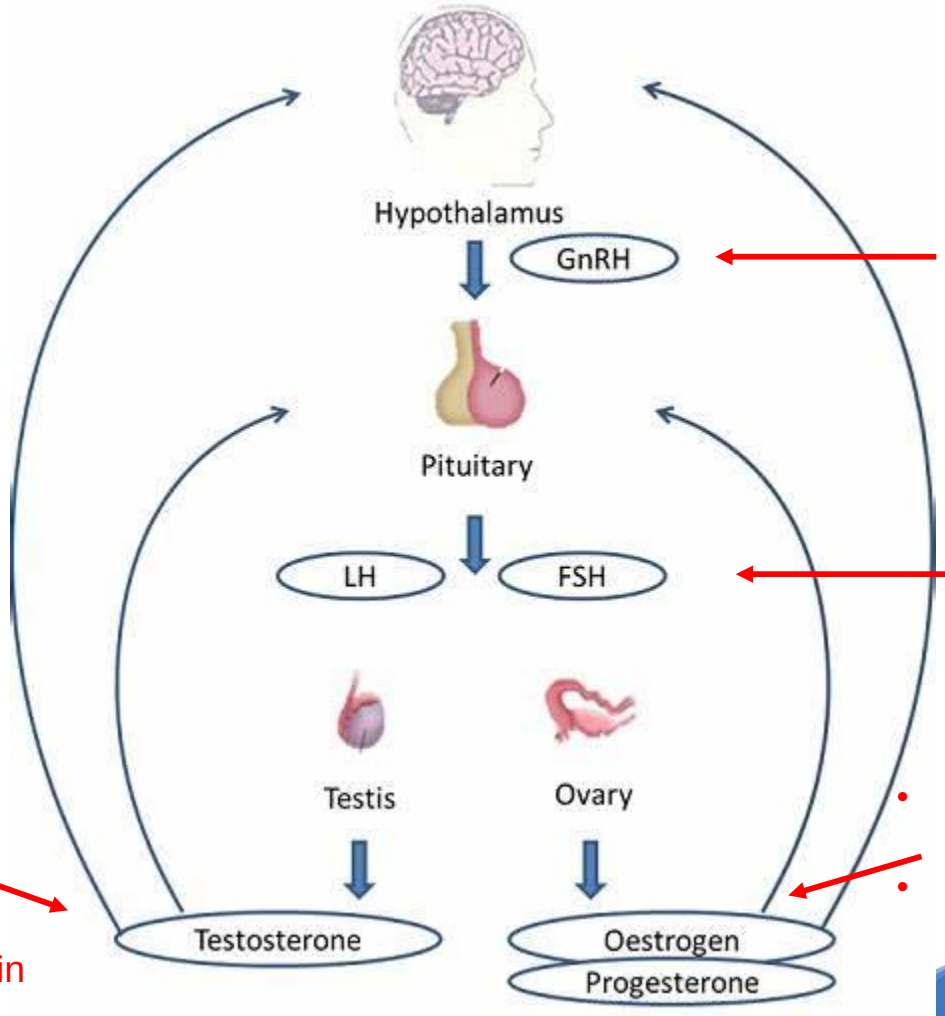
Prevalence unknown; evidence suggests as high as 90% amongst chronic opioid users

Hypothalamus-pituitary-gonad



Hypothalamus-pituitary-gonad

Puberty – attainment of secondary sexual characteristics and reproductive capabilities



Increasing amplitude
Pulsatile release

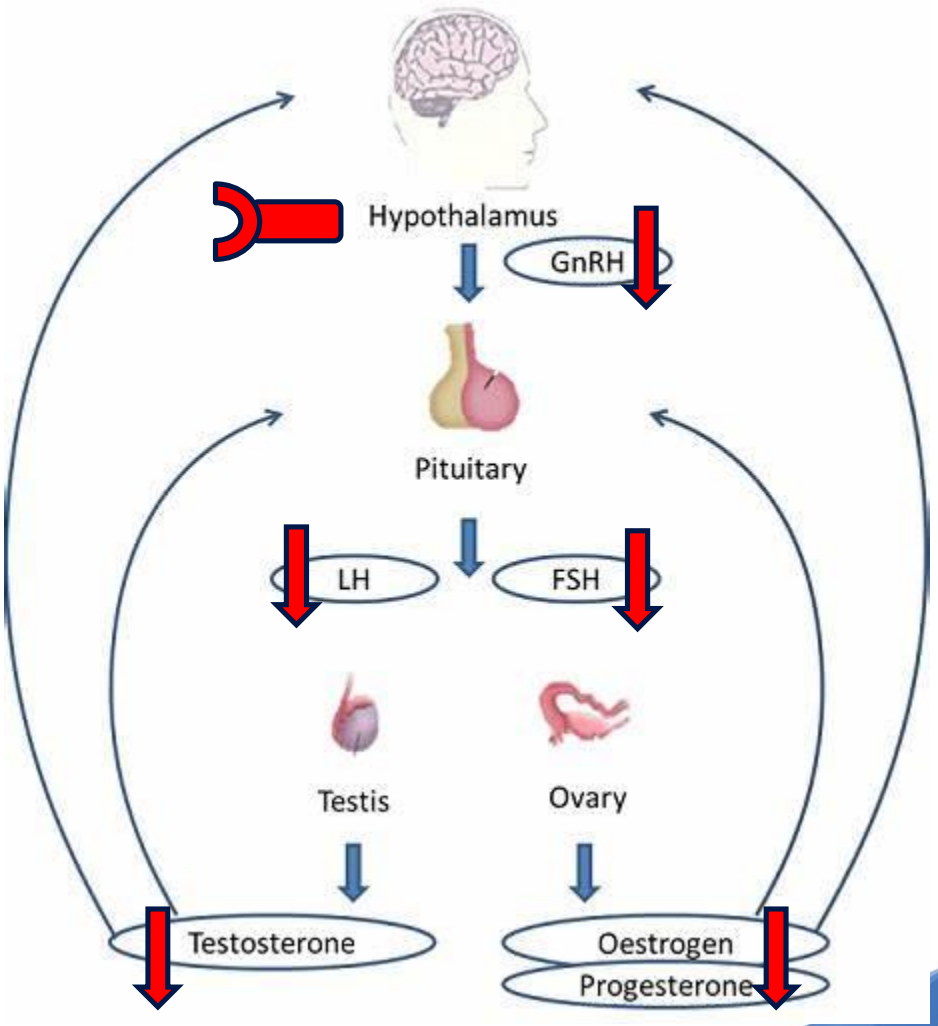
Increasing amplitude
Pulsatile release

- Stimulates pubertal changes in boys
- Stimulates secondary sexual characteristics in both sexes

- Stimulates breast and reproductive systems in girls
- Skeletal maturation and growth plate closure in both sexes

Hypothalamus-pituitary-gonad

Opioid



Broader health impacts of sex hormones

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Mood and cognition

Muscles and bones

Cardiovascular system

Sexual drive (libido)

Consequences of hypogonadism

Mood and cognition

Muscles and bones

Cardiovascular system

Sexual drive (libido)

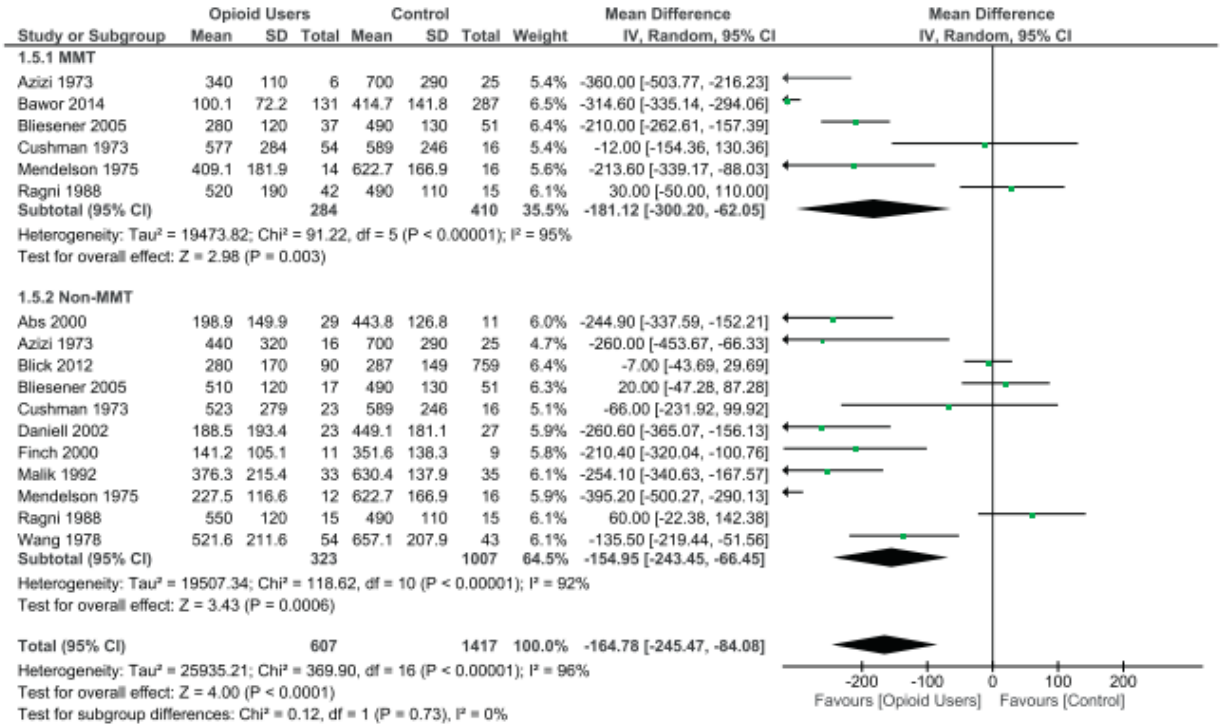
- Depressed mood
- Fatigue
- Sarcopenia (loss of muscle)
- Osteoporosis (loss of bone)
- Decreased libido
- Impotence, oligospermia (men)
- Infertility, menstrual irregularity (women)

Real world opioid therapy (1)

One meta-analysis (n = 2769) of a heterogenous 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



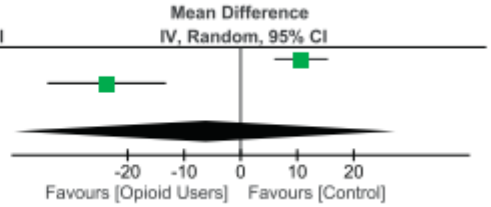
Study or Subgroup	Opioid Users Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 MMT								
Azizi 1973	340	110	6	700	290	25	5.4%	-360.00 [-503.77, -216.23]
Bawor 2014	100.1	72.2	131	414.7	141.8	287	6.5%	-314.60 [-335.14, -294.06]
Bliesener 2005	280	120	37	490	130	51	6.4%	-210.00 [-262.61, -157.39]
Cushman 1973	577	284	54	589	246	16	5.4%	-12.00 [-154.36, 130.36]
Mendelson 1975	409.1	181.9	14	622.7	166.9	16	5.6%	-213.60 [-339.17, -88.03]
Ragni 1988	520	190	42	490	110	15	6.1%	30.00 [-50.00, 110.00]
Subtotal (95% CI)			284			410	35.5%	-181.12 [-300.20, -62.05]
Heterogeneity: Tau² = 19473.82; Chi² = 91.22, df = 5 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 2.98 (P = 0.003)								
1.5.2 Non-MMT								
Abs 2000	198.9	149.9	29	443.8	126.8	11	6.0%	-244.90 [-337.59, -152.21]
Azizi 1973	440	320	16	700	290	25	4.7%	-260.00 [-453.67, -66.33]
Blick 2012	280	170	90	287	149	759	6.4%	-7.00 [-43.69, 29.69]
Bliesener 2005	510	120	17	490	130	51	6.3%	20.00 [-47.28, 87.28]
Cushman 1973	523	279	23	589	246	16	5.1%	-66.00 [-231.92, 99.92]
Daniell 2002	188.5	193.4	23	449.1	181.1	27	5.9%	-260.60 [-365.07, -156.13]
Finch 2000	141.2	105.1	11	351.6	138.3	9	5.8%	-210.40 [-320.04, -100.76]
Malik 1992	376.3	215.4	33	630.4	137.9	35	6.1%	-254.10 [-340.63, -167.57]
Mendelson 1975	227.5	116.6	12	622.7	166.9	16	5.9%	-395.20 [-500.27, -290.13]
Ragni 1988	550	120	15	490	110	15	6.1%	60.00 [-22.38, 142.38]
Wang 1978	521.6	211.6	54	657.1	207.9	43	6.1%	-135.50 [-219.44, -51.56]
Subtotal (95% CI)			323			1007	64.5%	-154.95 [-243.45, -66.45]
Heterogeneity: Tau² = 19507.34; Chi² = 118.62, df = 10 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 3.43 (P = 0.0006)								
Total (95% CI)			607			1417	100.0%	-164.78 [-245.47, -84.08]
Heterogeneity: Tau² = 25935.21; Chi² = 369.90, df = 16 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 4.00 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%								

Real world opioid therapy (2)

- No difference in testosterone levels observed in women

Study or Subgroup	Opioid Users Mean	SD	Total	Controls Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bawor 2014	36.6	23.2	100	25.9	15.2	496	51.0%	10.70 [5.96, 15.44]
Daniell 2008	30.7	21.5	21	54.4	10.3	16	49.0%	-23.70 [-34.19, -13.21]
Total (95% CI)			**121**			**512**	**100.0%**	**-6.17 [-39.87, 27.54]**

Heterogeneity: Tau² = 574.43; Chi² = 34.31, df = 1 (P < 0.00001); I² = 97%
Test for overall effect: Z = 0.36 (P = 0.72)



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¶

*The Byrne Surgery, Redfern, NSW, Australia, †School of Public Health, University of Sydney, NSW, Australia, ‡Australian Centre for Sexual Health, St. Leonards, NSW, Australia, §Specialist Diagnostic Services, North Ryde, NSW, Australia and ¶Centre for Clinical Epidemiology and Biostatistics, University of Newcastle, NSW, Australia

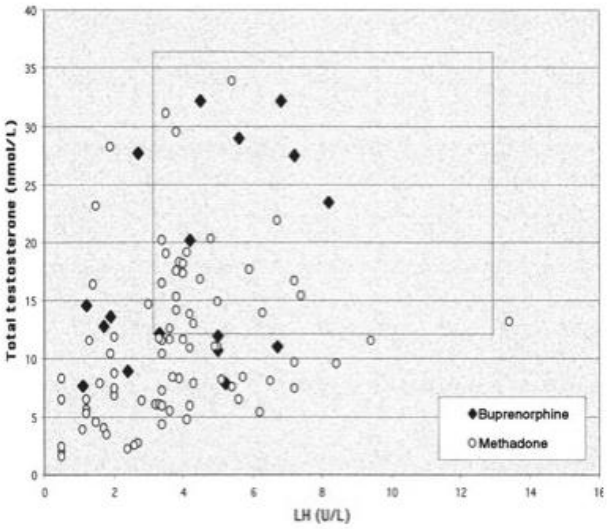


Figure 1 Total testosterone plotted against luteinising hormone (LH) for 17 buprenorphine treated men and 81 methadone treated men. Four men with incomplete data for LH and one outlier are excluded. The square zone represents the normal reference ranges for these hormones (Daniell, 2002a).

- 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)

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 (≥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)

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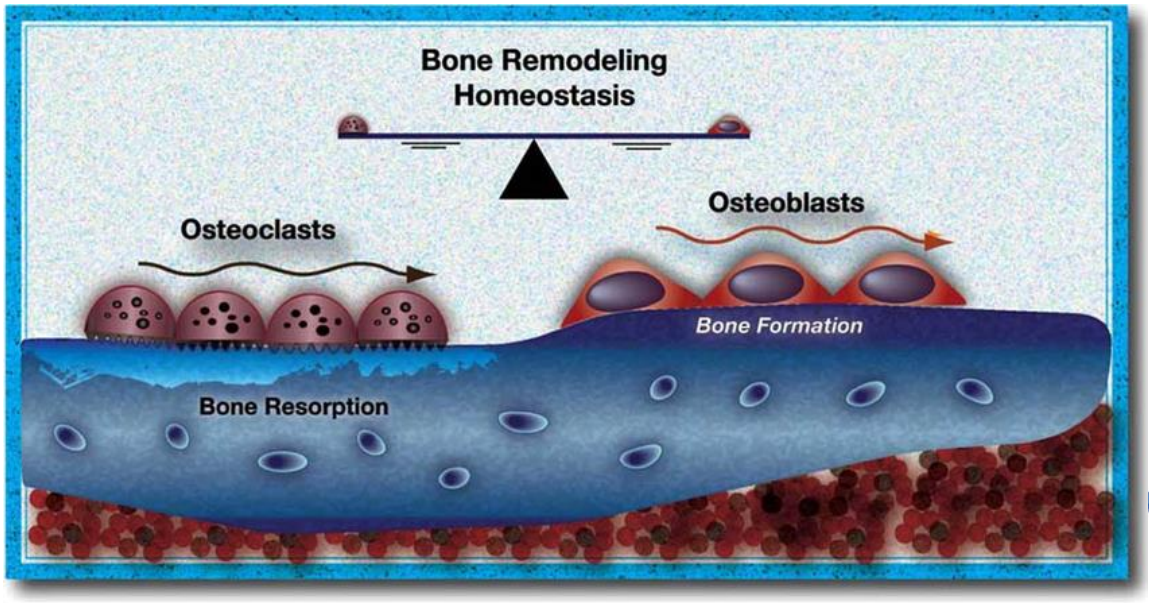
SKELETAL EFFECTS

Opioids and bone health

Opioids reduce Bone Mineral Density (BMD) and increase fracture risk

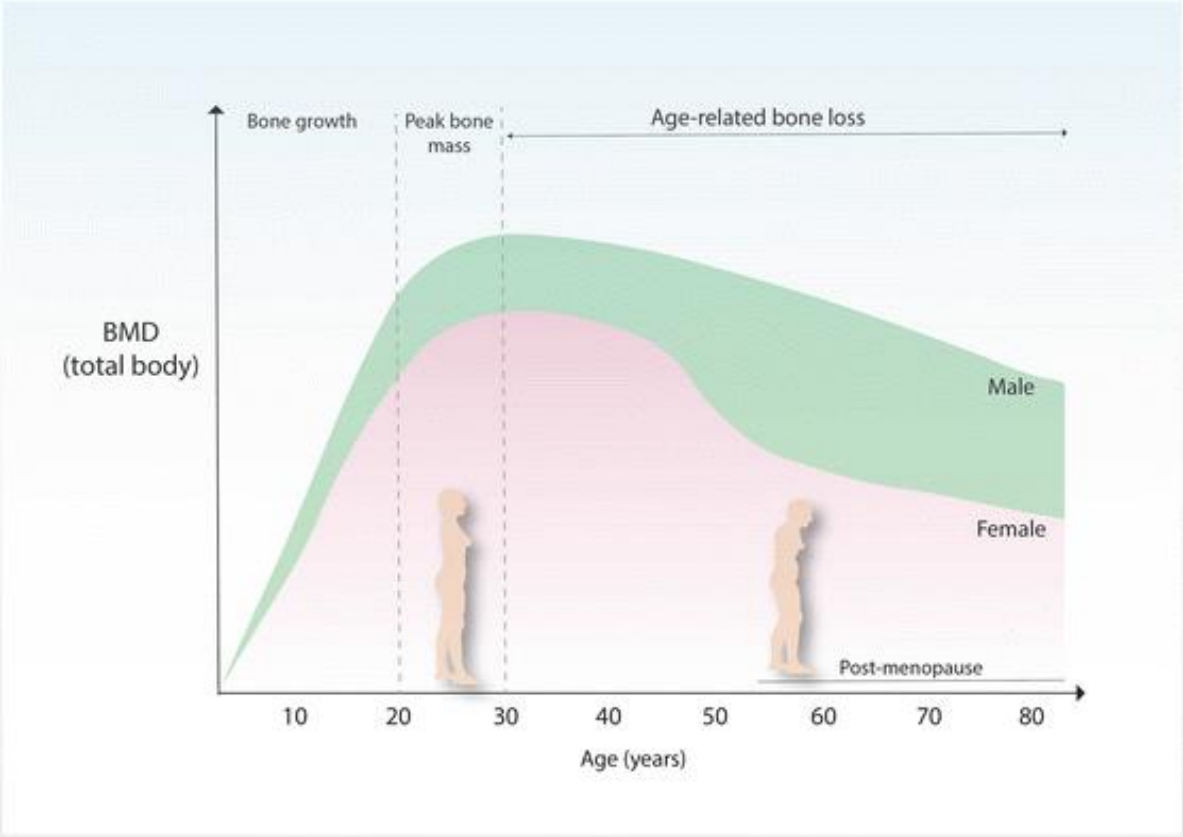
3 mechanisms

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



Adolescence and bone health

- Critical time for acquisition of peak bone mass
- Bone size and bone mineral content increase rapidly during late childhood and adolescence > continues to the beginning of the third decade of life



Real world opioid therapy (1)

(1) Different types of OAT including Buprenorphine increases the risk of osteoporosis (Gotthardt, 2017)

(2) Osteoporosis identified in up to 61% men and 20% women in a methadone program (n = 92) (Samet, 2006)

(3) Osteopenia identified in young women (age 21-29 years) on methadone program for <4 years (Eich, 2011)

(4) Meta-analysis indicates risk of fracture increased by up to 88% amongst all opioid users (Teng, 2015)

Real world opioid therapy (2)

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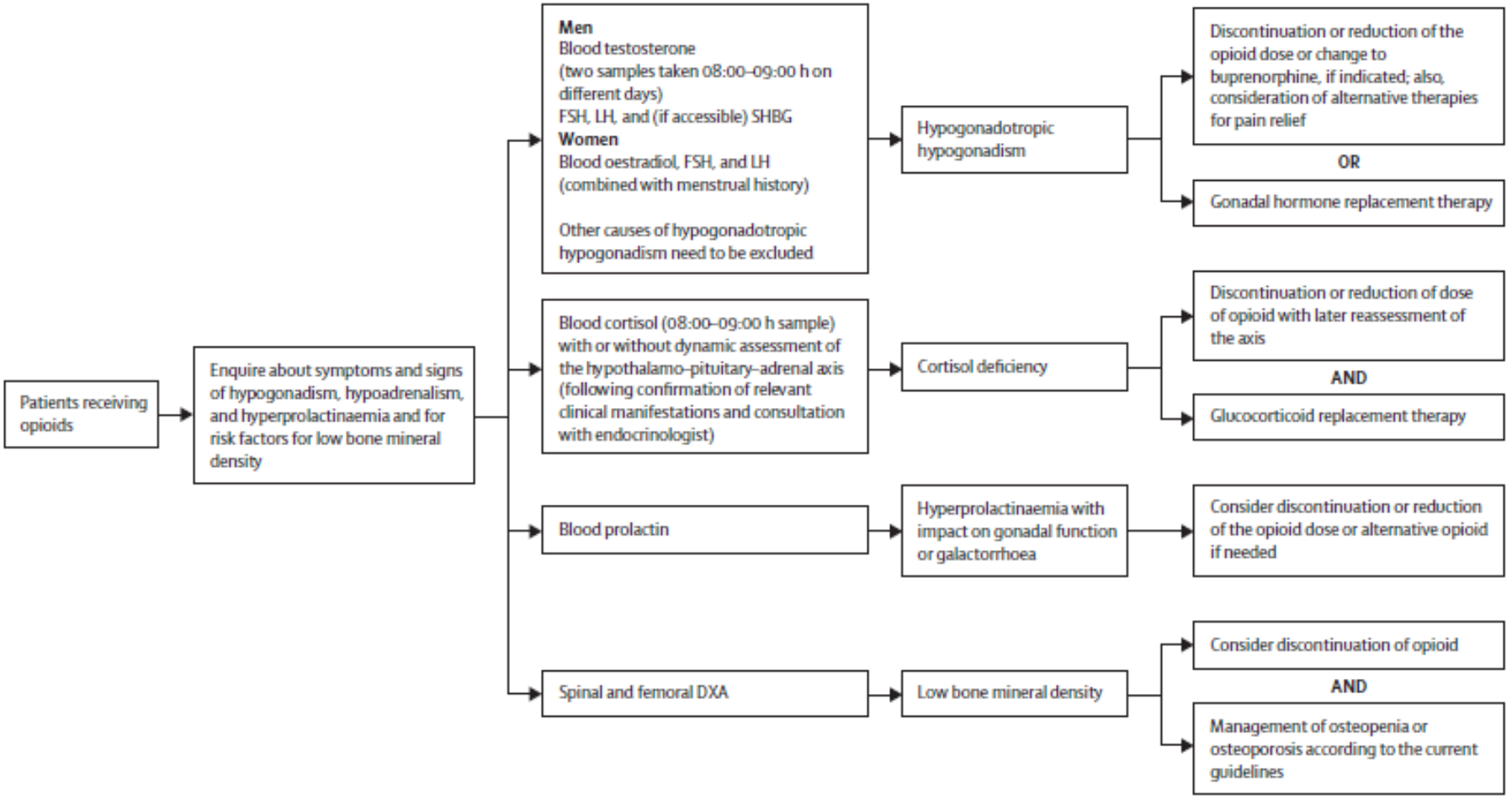
Focus on Buprenorphine

- Papers suggest buprenorphine has mixed effects on the endocrine system:
  - Transdermal buprenorphine had no effect on gonadal axis (Aurilio 2011)
  - Long-term buprenorphine on mice reduced plasma testosterone levels and damaged sperm production (Babaei 2011)
  - Suppresses gonadal axis in heroin users, but effects were smaller than with more potent opiates (Mendelson 1982)

- Long-term effects have not been adequately studied, especially in relation to LAIB in our population

SCREENING AND TREATMENT

Screening considerations



Fountas et al, Opioid-induced endocrinopathies, Lancet Diabetes Endocrinal 2020; 8:68-80

Treatment considerations

- Conflicting evidence regarding role of testosterone replacement therapy in men given risk of metabolic syndrome (hypertension, dyslipidaemia)
- One study suggests minimal benefit on quality life with no improvement in sleep quality, mood, sexual or physical function (AminiLari 2019)
- Another analysis of 21,272 long-term male opioid users indicated testosterone replacement therapy had lower all-cause mortality (Jasuja 2019)
- Limited evidence for hormone replacement for women with hypogonadism secondary to opioid therapy, but similar approach to menopausal hormone therapy is advised

Concluding remarks

- Given what we know about the long-term impacts of opioids, how should we monitor, counsel and manage our patients?
- What do you do currently in your own practice?
- How would you approach these discussions with adolescents who are already a difficult cohort to retain in treatment programs?

Conclusion

OAT saves lives and improves function

Need to monitor long-term physical effects of opioid exposure

Partial agonism better than full agonism