# Complications of Long-Term Opiate Use


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# Objectives:

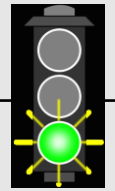
- Review long term effects of opiate use and provide a topical review of the evidence to support these assertions
  - Immediate side effects can have long term consequences
  - Endocrinopathies
  - Metabolic dysfunction
  - Immunopathies
  - Hyperalgesia
- Highlight potential ways to manage long term effects of chronic opiate use
- Discuss alternatives to chronic opiate use
- Provide practical information to hopefully enrich clinical practice

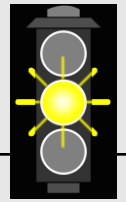
# Examples of Opiates

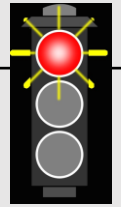
**Full Agonists**
oxycodone
Percocet
Norco
hydrocodone
morphine
Dilaudid
fentanyl
heroin

**Partial Agonists**
Butrans
buprenorphine
Suboxone

**Antagonists**
naloxone
narcan





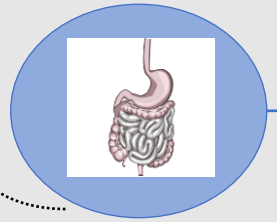


Mu Receptor

# Immediate Effects of Opiates

- Analgesia (Pain relief)
- Impaired Thinking
- Impaired Decision Making
- Decreased Consequence Awareness
- Euphoria
- Respiratory Depression

- Dry Mouth



- Constipation

# Opiate-Induced Xerostomia

"The main function of saliva is not—as is commonly believed—to aid in digestion, but to protect the integrity of the oral tissues. The ability of saliva to limit the growth of pathogens—and in some instances even preventing them from establishing a niche in the biofilm community in the first place—is a major determinant of general, as well as oral, health. **When salivary flow is compromised, the gateway to the body can open wide to local as well as to systemic pathogens**."

Oral Health in America: A Report of the Surgeon General-Executive Summary. Rockville. MD: U.S. Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health. 2000.

# Opiate-Induced Xerostomia

**Caries management by risk assessment: implementation guidelines**

- Refer
- Remineralize
- Hydrate
- Lubricate
- Restore

Caries management by risk assessment: implementation guidelines November 2007 Journal of the California Dental Association 35(11):799-805

# Opiate-Induced Dry Eye Disease

## CLINICAL SIGNIFICANCE

Dry eye disease (DED), particularly when severe, can have a significant impact on visual acuity, daily activities, social and physical functioning, and workplace productivity.

## First line treatments

- Tear supplementation
- Environmental coping strategies
- Application of warm compresses
- Discontinuation of systemic or ocular medications that can contribute to dryness, if possible

Patients who do not obtain adequate relief from tear supplementation or environmental adjustment should be referred to an ophthalmologist.

https://www.uptodate.com/contents/dry-eye-disease?search=dry%20eyes&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H22

# Opiate-Induced Constipation

**Common strategies for managing opioid-induced constipation**

| |
|---|
| **1. Nonpharmacologic approaches for all patients, unless contraindicated by medical status** |
| Increase fluid intake |
| Increase dietary soluble fiber (avoid if severely debilitated or bowel obstruction is suspected) |
| Encourage mobility |
| Ensure comfort and privacy for defecation |
| **2. Select a pharmacologic strategy*** |
| Intermittent use of a rectal therapy, either a suppository such as bisacodyl or glycerin, or mineral oil and/or sodium phosphate enema |
| Intermittent use (every 2-3 days) of an osmotic laxative, such as polyethylene glycol, magnesium hydroxide, or magnesium citrate |
| Trial of a daily softening agent (docusate) |
| Intermittent use (every 2-3 days) of a contact cathartic, such as senna or bisacodyl |
| Daily use of a contact cathartic (with or without a concurrent softening agent) |
| Daily use of lactulose (unless lactose-intolerant) or sorbitol |
| Daily use of polyethylene glycol |
| **3. Adjust dose and dosing schedule of selected therapy to optimize effects** |
| **4. Switch or combine conventional approaches if initial therapy is inadequate** |
| **5. Consider adding a peripheral opioid antagonist (eg, methylnaltrexone, naloxegol, or an opioid-naloxone fixed combination) or lubiprostone; if constipation continues to be refractory, consider alternative drugs, eg, metoclopramide.** |

*Fiber supplements and/or bulk-forming laxatives (eg, psyllium) are an option for treating non-debilitated patients who maintain good oral hydration; however, efficacy is generally modest in patients with slow transit constipation, who are also more likely to experience bloating and distention. If used, patients should start with small amounts of fiber or bulking laxatives and increase gradually as tolerated.

UpToDate®

https://www.uptodate.com/contents/prevention-and-management-of-side-effects-in-patients-receiving-opioids-for-chronic-pain?search=oic&source=search_result&selectedTitle=1~41&usage_type=default&display_rank=1#H1092358653

# Side Effects of Chronic Opiate Use

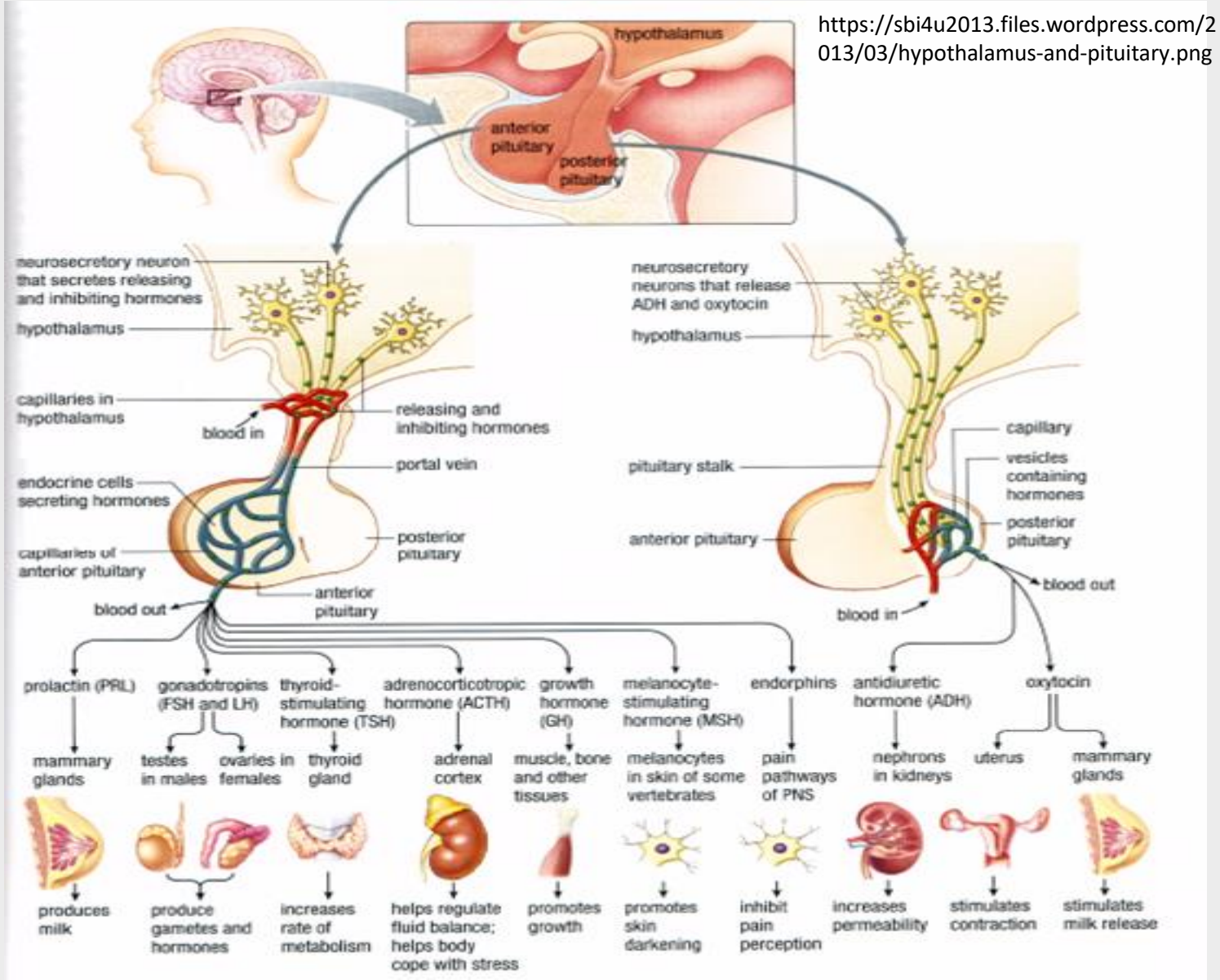
- Endocrinopathies
- Metabolic dysfunction
- Immunopathy
- Hyperalgesia

# Endocrinopathies

- Hypogonadism
- Adrenal insufficiency
- Osteoporosis
- Metabolism and glycemic control

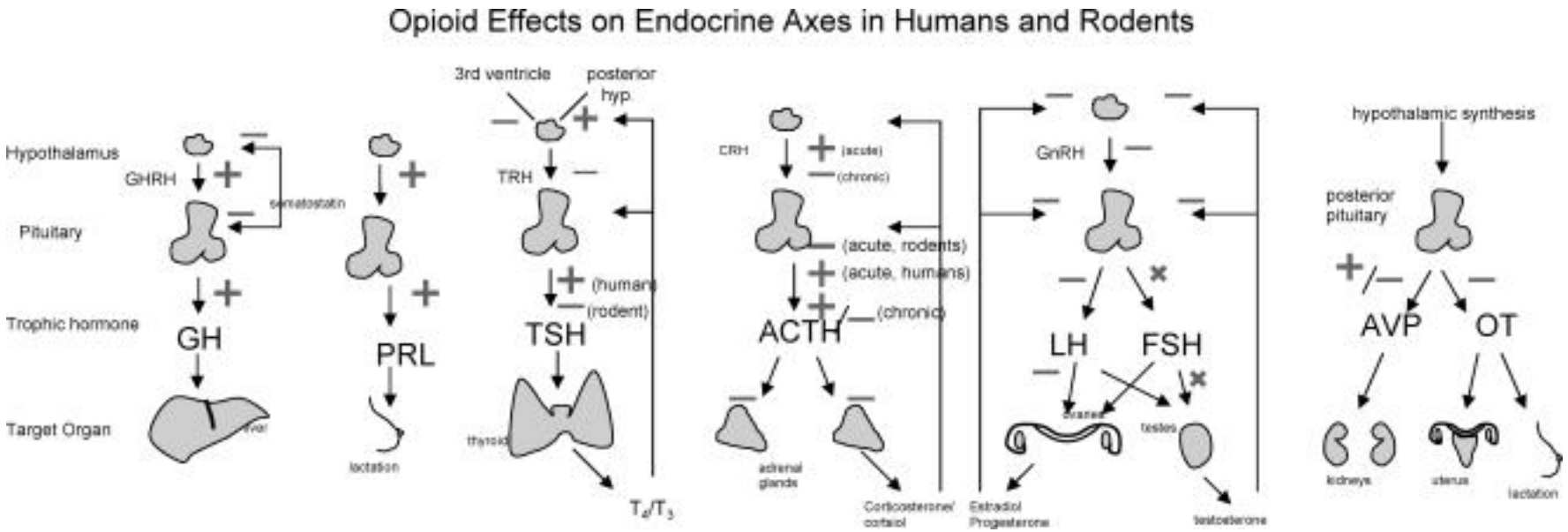
# HPA Neuroendocrine Review

https://sbi4u2013.files.wordpress.com/2013/03/hypothalamus-and-pituitary.png




Antony, T, Alzaharani, SY, El-Ghaiesh, SH. Opioid-induced hypogonadism: Pathophysiology, clinical and therapeutics review. *Clin Exp Pharmacol Physiol*. 2020; 47: 741– 750. https://doi.org/10.1111/1440-1681.13246

# Opiate-Induced Neuroendocrine Dysfunction




Vuong C, Van Uum SH, O'Dell LE, Lutfy K, Friedman TC. The effects of opioids and opioid analogs on animal and human endocrine systems. *Endocr Rev*. 2010;31(1):98-132. doi:10.1210/er.2009-0009

# Opiate-Induced Neuroendocrine Dysfunction: Adrenal Insufficiency

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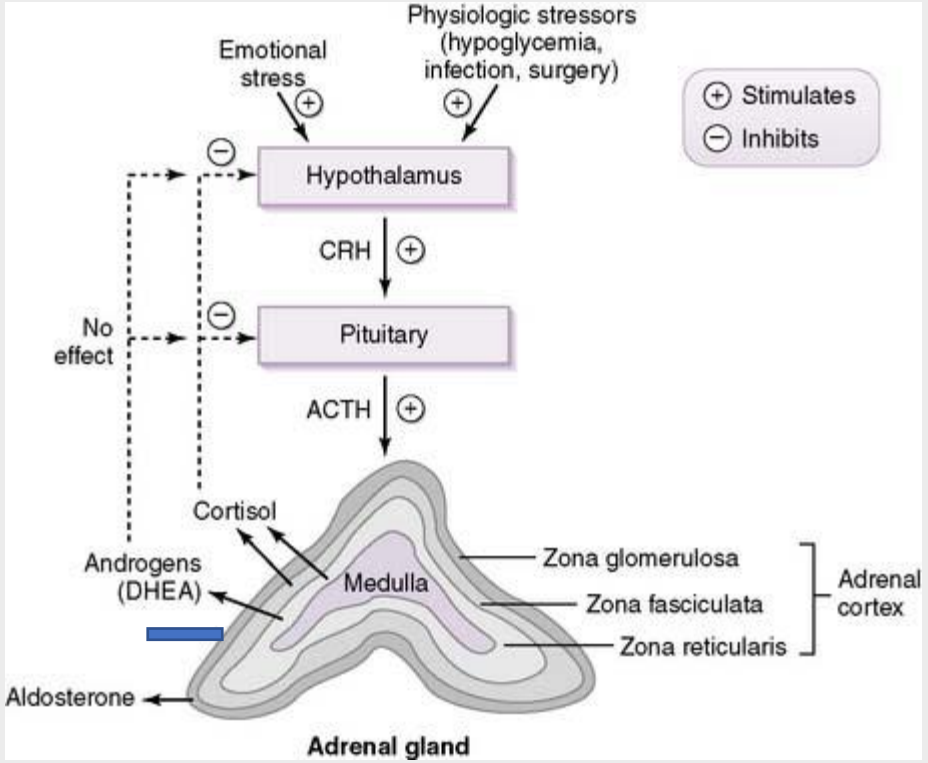



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Daniell HW. DHEAS deficiency during consumption of sustained-action prescribed opioids: evidence for opioid-induced inhibition of adrenal androgen production. *J Pain*. 2006;7(12):901-907. doi:10.1016/j.jpain.2006.04.011

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Primary vs. Secondary

**Hypogonadism in a male** refers to a decrease in either or both of the two major functions of the testes: sperm production and testosterone production:

- <u>disease of the testes (primary hypogonadism)</u>
  - The patient has primary hypogonadism if his serum testosterone concentration and/or sperm count are low and/or his serum LH and FSH concentrations are high.

- <u>disease of the pituitary or hypothalamus (secondary hypogonadism)</u>
  - The patient has secondary hypogonadism if his serum testosterone concentration and/or the sperm count are low and/or his serum LH and FSH concentrations are not elevated, as they would be if gonadotroph cell function were normal.

https://www.uptodate.com/contents/prevention-and-management-of-side-effects-in-patients-receiving-opioids-for-chronic-pain?search=opiate%20induced%20hypogonadism&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H13

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Roll of Mu Receptor

- In patients on chronic opioids, it is speculated that there is both central and peripheral inhibition of this process.
- Centrally, opioids are thought to inhibit the GnRH release from the hypothalamus by binding μ receptors. Multiple studies have shown that opioids inhibit GnRH release and testosterone production, referred to as opioid-induced androgen deficiency (OPIAD).

Duarte RV, Raphael JH, Southall JL, Labib MH, Whallett AJ, Ashford RL. Hypogonadism and low bone mineral density in patients on long-term intrathecal opioid delivery therapy. *BMJ Open*. 2013;3(6).

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Prolactin & GnRH

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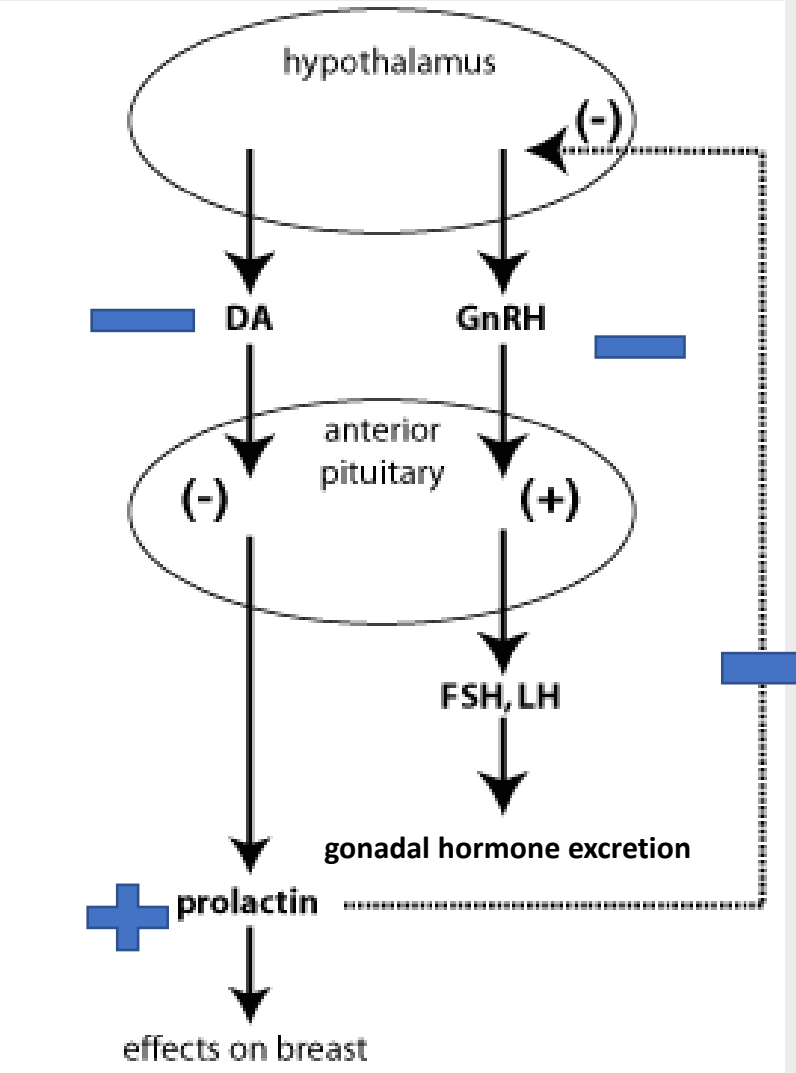


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# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, GnRH & Testosterone

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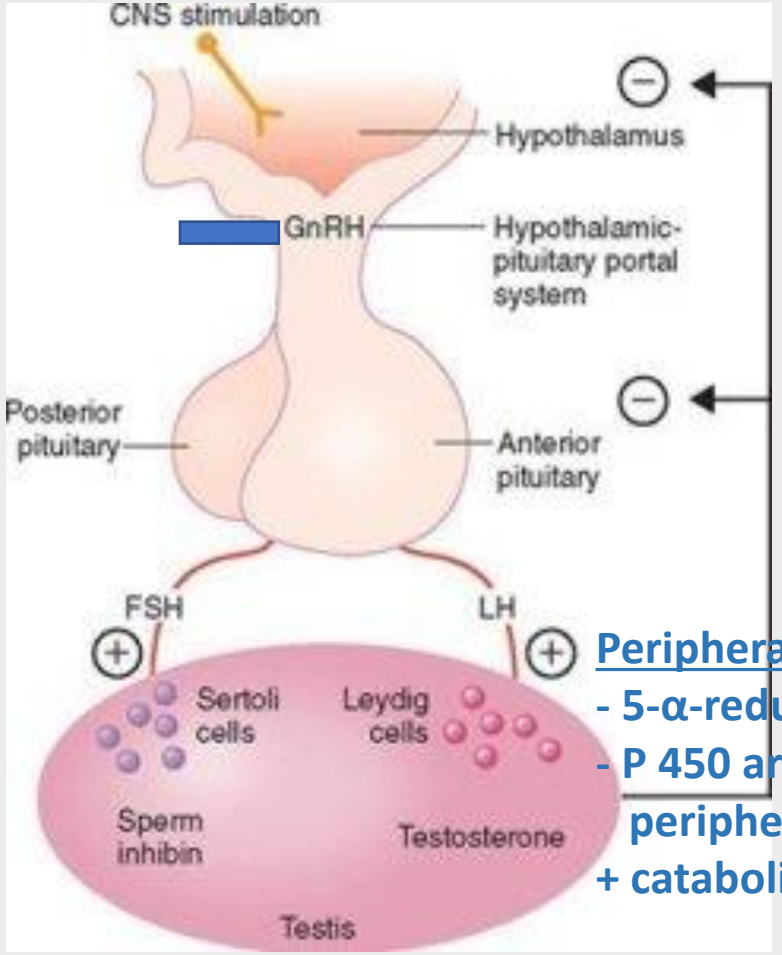


**Peripheral:**
**- 5-α-reductase**
**- P 450 aromatase mRNA in peripheral body tissues**
**+ catabolism of testosterone**

Antony, T, Alzaharani, SY, El-Ghaiesh, SH. Opioid-induced hypogonadism: Pathophysiology, clinical and therapeutics review. *Clin Exp Pharmacol Physiol*. 2020; 47: 741– 750. https://doi.org/10.1111/1440-1681.13246

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Clinical Symptoms

**TABLE 2** Presenting symptoms of hypogonadism

| | Males | Females | Reference |
|---|---|---|---|
| Depression and anxiety | √ | √ | 107-110 |
| Tiredness and fatigability | √ | √ | 77-79 |
| Decreased muscle mass and weakness | √ | √ | 91 |
| Diminished libido | √ | √ | 47,48,54,57-59,85 |
| Infertility | √ | √ | 111,112 |
| Diminished bone mineral density | √ | √ | 88,89,113-115 |
| Hot flashes and night sweating | √ | √ | 116,117 |
| Diminished opioid analgesia (pain) | √ | √ | 49,117,118 |
| Amenorrhea/irregular menses | -- | √ | 85 |
| Hyperprolactinemia | -- | √ | 52,71,81,119,120 |
| Erectile dysfunction | √ | -- | 121-124 |

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# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Incidence

- CONCLUSION: hypogonadism occurs in more than half of the male chronic opioid users, and hypocortisolism in approximately a fifth of all patients.
  - Mees Bruin, BSc, Friso de Vries, PhD, Olaf Dekkers, MD, Jan Schoones, MA, Wouter van Furth, MD, Alberto Pereira, MD, Niki Karavitaki, MD, Nienke Biermasz, MD, Amir Zamanipoor Najafabadi, PhD, SUN-489 Opioid Epidemic and Related Endocrine Effects: A Systematic Review and Meta-analysis., *Journal of the Endocrine Society*, Volume 3, Issue Supplement_1, April-May 2019, SUN–489, https://doi.org/10.1210/js.2019-SUN-489

- CONCLUSION: the incidence of osteoporosis in hypogonadal men to be as high as 50%.
  - Brennan MJ. The effect of opioid therapy on endocrine function. *Am J Med*. 2013; 126(3 Suppl 1):S12-18.

# Opiate-Induced Neuroendocrine Dysfunction: Dose-Dependent Hypogonadism

- **Hormone levels averaged much lower in opioid users than in control subjects in a dose-related pattern** (P <.0001 for all comparisons). FT, TT, and E levels were subnormal in 56%, 74%, and 74%, respectively, of opioid consumers. Forty-eight men (89%) exhibited subnormal levels of either FT or E . Either TT or E level was subnormal in all 28 men consuming the equivalent of 100 mg of methadone daily and in 19 of 26 (73%) consuming smaller opioid doses.
- **Eighty-seven percent of opioid-ingesting men who reported normal erectile function before opioid use reported severe erectile dysfunction or diminished libido after beginning their opioid therapy**.

Harry W. Daniell, Hypogonadism in men consuming sustained-action oral opioids, The Journal of Pain, Volume 3, Issue 5, 2002, Pages 377-384, ISSN 1526-5900, https://doi.org/10.1054/jpai.2002.126790. (http://www.sciencedirect.com/science/article/pii/S1526590002000329)

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Immediate Suppression

- Case study: showed an undetectable concentration of serum cortisol and a suppressed concentration of testosterone; therefore, he was referred urgently with a diagnosis of hypopituitarism**. We elicited a history that he had been treated with opiate analgesics for 3 days at the time of his original blood tests**. We conclude that his morphine therapy had caused profound suppression of his HPA and pituitary-gonadal

Policola C, Stokes V, Karavitaki N, Grossman A. Adrenal insufficiency in acute oral opiate therapy. *Endocrinol Diabetes Metab Case Rep*. 2014;2014:130071. doi:10.1530/EDM-13-0071

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Immediate and Long Term Testosterone Suppression & T-independent bone pathology

- **Methods:** A femoral osteotomy was created in 75 Sprague-Dawley rats. Postoperatively, animals were randomized into three treatment groups: control, morphine, and morphine plus testosterone. Testosterone levels were recorded preoperatively and at 48 hours, 4 weeks, and 8 weeks postoperatively. Some animals were euthanized at 4 weeks and others at 8 weeks postoperatively. Histology and micro-CT scans were used to evaluate callus. Three-point bend testing was performed to evaluate callus strength.
- **Results:** Serum testosterone levels in the morphine group showed decreased baseline levels of 2.2 ng/mL, 1.4 ng/mL, and 1.4 ng/mL ($p < 0.001$), whereas the morphine plus testosterone supplementation group showed increased serum levels at 41.7 ng/mL, 11.8 ng/mL, and 19.8 ng/mL ($p < 0.001$) compared with control animals (3.3 ng/mL, 5.8 ng/mL, 5.2 ng/mL) at 48 hours, 4 weeks, and 8 weeks, respectively. Compared with control animals, histology and micro-CT showed an impedance of callus maturation in the two experimental groups. Morphine-treated animals showed reduction in callus strength at 8 weeks (30% of the contralateral unfractured femur strength compared with 49% seen in the control animals at 8 weeks; $p = 0.048$); this finding was not fully reversed by testosterone supplementation (33% of the contralateral femur strength; $p = 0.171$).
- **Conclusions:** Opioid-induced androgen deficiency occurred in this orthopaedic animal model. Although we previously showed that morphine inhibits callus maturation, the current study did not show a rescue of the morphine-treated animals with testosterone supplementation in either morphologic or mechanical testing. Testosterone suppression associated with opioid administration occurred almost immediately (within 48 hours) and was suppressed continually throughout the 8-week duration of study.

Chrastil J, Sampson C, Jones KB, Higgins TF. Evaluating the affect and reversibility of opioid-induced androgen deficiency in an orthopaedic animal fracture model. *Clin Orthop Relat Res*. 2014;472(6):1964-1971. doi:10.1007/s11999-014-3517-x

# Opiate-Induced Neuroendocrine Dysfunction: Independent Osteoporosis

**Direct Osteoblast Inhibition**

- Another peripheral effect that opioids may exert on bone density relates to osteoblast function. It has been theorized that osteoblast function is inhibited through binding of opioids to μ receptors on osteoblasts. Inhibition of osteoblasts causes decreased synthesis of new bone, which can cause a decrease in bone density. Osteocalcin is used as a biomarker for osteoblast activity. It has been shown to be decreased in patients taking chronic opioids
    - Brennan MJ. The effect of opioid therapy on endocrine function. *Am J Med*. 2013; 126(3 Suppl 1):S12-18.

- In the study, 81 men on both acute to long-term opioid therapy had blood samples and bone scans performed. The researchers found a discrepancy between the percentage of men with hypogonadism (27%) and the percentage of with osteopenia/osteoporosis (44%), suggesting that monitoring for total testosterone levels is not a reliable method to determine the risk for developing opioid-associated osteoporosis.
    - Fortin JD, Bailey GM, Vilensky JA. Does opioid use for pain management warrant routine bone mass density screening in men? *Pain Physician*. 2008;11(4):539-541.

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Bone Health

- Bone mineral density and remodeling is under crucial mechanisms involving hormonal contributory mainly sex hormones. Androgens and estradiol play a pivotal role in bone health and equilibrate bone remodeling status.
- Patients on long-term opioids are reported as more prone to fracture due to dizziness.
- Opioid Receptor activation of nuclear factor κ-B (RANKL) has been recently linked to bone remodeling via the suppression of osteoclast differentiation through non-genomic mechanisms.

Antony, T, Alzaharani, SY, El-Ghaiesh, SH. Opioid-induced hypogonadism: Pathophysiology, clinical and therapeutics review. *Clin Exp Pharmacol Physiol*. 2020; 47: 741–750. https://doi.org/10.1111/1440-1681.13246

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Osteoporosis

- Gender has shown to have a varying effect on the risk for developing opioid-induced osteopenia/osteoporosis. In one study, men and women both develop premature osteoporosis that was thought to be caused by chronic opioid use. Women demonstrated bone densities in the osteoporotic range prior to age 40 at a much higher rate than expected. Men in the study frequently had testosterone levels <50 ng/dL (in the male castrate range), which was associated with osteopenia.

Daniell H. Opioid osteoporosis. *Arch Intern Med*. 2004;164(3):338

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism

## Osteoporosis

- In the study, by Grey et al, men had a 10% lower bone density as compared to controls, whereas women had bone densities approaching those of the age-matched general population.
- The 10% lower bone mineral density is associated with a 2-fold increase in the relative risk of fractures in this population.

Grey A, Rix-Trott K, Horne A, Gamble G, Bolland M, Reid IR. Decreased bone density in men on methadone maintenance therapy. *Addiction*. 2011;106(2):349-354

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Male Osteoporosis Guidelines

## Endocrine Society Clinical Practice Guideline

- We recommend testing higher risk men [**aged ≥70 and men aged 50–69 who have risk factors** (e.g. low body weight, prior fracture as an adult, smoking, etc.)] using central dual-energy x-ray absorptiometry.
- **Adequate calcium and vitamin D and weight-bearing exercise should be encouraged; smoking and excessive alcohol should be avoided**.
- Pharmacological treatment is recommended for men aged 50 or older who have had spine or hip fractures, those with T-scores of −2.5 or below, and men at high risk of fracture based on low bone mineral density and/or clinical risk factors.
- Treatment should be monitored with serial dual-energy x-ray absorptiometry testing.

**Full Guideline:** Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline ***JCEM June 2012*** Nelson B. Watts, Robert A. Adler, John P. Bilezikian, Matthew T. Drake, Richard Eastell, Eric S. Orwoll, Joel S. Finkelstein

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism, Male Testosterone Replacement

**Endocrine Society Clinical Practice Guideline**

- Recommends making a diagnosis of hypogonadism only in men with symptoms and signs consistent with testosterone (T) deficiency and unequivocally and consistently low serum T concentrations.
- Recommend confirming the diagnosis by repeating the measurement of morning fasting total T concentrations.
- We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.
- **We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level >4 ng/mL, a prostate-specific antigen level >3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia.**
- In hypogonadal men 55 to 69 years old, who are being considered for testosterone therapy and have a life expectancy >10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision making regarding prostate cancer monitoring. **For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone**. In hypogonadal men being considered for testosterone therapy who are 40 to 69 years old and at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer), we suggest discussing prostate cancer risk with the patient and offering monitoring options.
- **We suggest against routinely prescribing testosterone therapy to all men 65 years or older** with low testosterone concentrations. In men 65 years who have symptoms or conditions suggestive of testosterone deficiency (such as low libido or unexplained anemia) and consistently and unequivocally low morning testosterone concentrations, we suggest that clinicians offer testosterone therapy on an individualized basis after explicit discussion of the potential risks and benefits.

**Full Guideline:** Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline ***JCEM | March 2018*** Shalender Bhasin, Juan P. Brito, Glenn R. Cunningham, Frances J. Hayes, Howard N. Hodis, Alvin M. Matsumoto, Peter J. Snyder, Ronald S. Swerdloff, Frederick C. Wu, Maria A. Yialamas

# Opiate-Induced Neuroendocrine Dysfunction: Hypogonadism in Women

Our observations document **hypogonadotrophic hypogonadism plus decreased adrenal androgen production in most women consuming sustained-action oral or transdermal opioids.**

- **Testosterone, estradiol, and dehydroepiandrosterone sulfate values were 48% to 57% lower** in opioid-consuming women with intact ovarian tissue than in control subjects ($P < .01$-$.05$).
- **Luteinizing hormone and follicle-stimulating hormone values averaged 30% lower in premenopausal and 70% lower in postmenopausal opioid consumers** ($P < .001$). Among oophorectomized women not consuming estrogen, free testosterone levels were 39% lower in opioid consumers ($P < .05$), indicating impaired adrenal androgen production.
- Additional lowering of free testosterone levels was associated independently with oral estrogen replacement and low body mass index.
- **Menses had often ceased soon after beginning sustained-action opioid therapy.**

Daniell HW. Opioid endocrinopathy in women consuming prescribed sustained-action opioids for control of nonmalignant pain. *J Pain*. 2008;9(1):28-36. doi:10.1016/j.jpain.2007.08.005

# Opiate-Induced Neuroendocrine Dysfunction: Poor Glycemic Control

- **Weight gain and abnormal glycemic control** — Studies of patients receiving methadone therapy for addiction have noted an association between this opioid and weight gain.
- Both hyperglycemia and hypoglycemia have been observed in patients using opiates

Methadone Use and the Risk of Hypoglycemia for Inpatients With Cancer Pain.AUFlory JH, Wiesenthal AC, Thaler HT, Koranteng L, Moryl N SOJ Pain Symptom Manage. 2016;51(1):79. Epub 2015 Sep 3.

# Opiates suppress the Immune System

- Infections
- Cancer
- Wound healing

# Opiate-Induced Immunosuppression in Infections, Pathophysiology

- opioids and cannabinoids have been found to be immunosuppressive, both in vitro and in vivo in a variety of assays, including response of:
  - lymphocytes to mitogens,
  - antibody formation,
  - activation of T-cells,
  - Natural Killer Cell activity,
  - phagocytosis by macrophages and neutrophils.
- Drugs in these two classes have also been shown to inhibit migration of cells from the circulatory system to areas of inflammation, including passage across the blood-brain barrier.
- Opioids and cannabinoids have both been shown to sensitize mice to a variety of infectious agents
  - In specialized rodent models and in monkeys, opioids sensitized to HIV

Eisenstein T.K., Rogers T.J. (2017) Drugs of Abuse. In: Ikezu T., Gendelman H. (eds) Neuroimmune Pharmacology. Springer, Cham

# Opiate-Induced Immunosuppression, Roll of the Mu Receptor

Naltrexone blocked morphine-induced analgesia and immunosuppression in a dose-dependent fashion. Moreover, the combination of 1.0 mg/kg of naltrexone and 32.0 mg/kg of morphine elevated splenic NK activity. A large dose of morphine (100.0 mg/kg) elicited full analgesia and had no effect on splenic NK activity in saline- or naltrexone-pretreated mice. Collectively, these results support the view that, in mice, morphine-induced analgesia and immunosuppression are mediated through a common opioid receptor type.

Carr DJ, Gerak LR, France CP. Naltrexone antagonizes the analgesic and immunosuppressive effects of morphine in mice. *J Pharmacol Exp Ther*. 1994;269(2):693-698.

# Opiate-Induced Immunosuppression, Roll of the Mu Receptor

- Two hours after a subcutaneous injection of morphine (25 mg/kg), blood lymphocyte proliferation was found to be 70% depressed, compared to saline-injected controls. This effect was partially antagonized in animals pretreated with naltrexone (10 mg/kg)
- The administration of morphine did result in a 30-40% inhibition of cytolytic activity of natural killer cells, which was completely antagonized in naltrexone-pretreated animals.
- Naltrexone alone was found to have no effect on either proliferation of blood and splenic lymphocytes or the cytolytic activity of splenic lymphocytes.
- Although naltrexone had no effect on the activity of lymphocytes, animals treated with either naltrexone or morphine alone, or their combination, had 4- to 8-fold increases in corticosterone in plasma. These results demonstrate that the accompanying increase in circulating levels of corticosterone most likely did not contribute to these effects.

Bayer BM, Daussin S, Hernandez M, Irvin L. Morphine inhibition of lymphocyte activity is mediated by an opioid dependent mechanism. *Neuropharmacology*. 1990;29(4):369-374. doi:10.1016/0028-3908(90)90096-a

# Opiate-Induced Immunosuppression, Roll of the Mu Receptor

- Abolition of morphine-immunosuppression in mice lacking the mu-opioid receptor gene (MOR)
- Chronic morphine administration induced lymphoid organ atrophy, diminished the ratio of CD4 CD8 cells in the thymus and strongly reduced natural killer activity in wild-type mice.
- None of these effects was observed in MOR-deficient mice after morphine treatment. This demonstrates that the MOR gene product represents a major molecular target for morphine action on the immune system

Gavériaux-Ruff C, Matthes HW, Peluso J, Kieffer BL. Abolition of morphine-immunosuppression in mice lacking the mu-opioid receptor gene. *Proc Natl Acad Sci U S A*. 1998;95(11):6326-6330. doi:10.1073/pnas.95.11.6326

# Opiate-Induced Immunosuppression in Infections, Variable Effects

Current opioid use was associated with a 38 percent greater risk for community-acquired pneumonia compared with nonuse. Risk was highest for opioids characterized as immunosuppressive based upon preclinical studies (ie, morphine but not hydromorphone or oxycodone) and for use of long-acting opioids (OR 3.43, 95% CI 1.44-8.21) but not short-acting opioids (OR 1.27, 95% CI 0.98-1.64).

Dublin S, Walker RL, Jackson ML, Nelson JC, Weiss NS, Von Korff M, Jackson LA SOJ Am Geriatr Soc. 2011;59(10):1899. Epub 2011 Sep 13.

# Opiate-Induced Immunosuppression in Infections, Variable Effects

- METHODS: We conducted a retrospective cohort study of Tennessee Medicaid enrollees to compare the infection risk among patients using long-acting **opioids with known immunosuppressive properties (morphine, fentanyl, methadone)** to the infection risk among patients using long-acting **opioids without known immunosuppressive properties (oxycodone, oxymorphone, tramadol**). We further compared users of individual long-acting opioids to long-acting morphine users (considered the prototypical immunosuppressive opioid).
- RESULTS: Nonimmunosuppressive opioid users had a lower rate of infections than immunosuppressive opioid users (aIRR:0.78 [CI: 0.66-0.91]). Among individual opioids, oxycodone users had a lower rate of infection than morphine users (aIRR:0.73 [CI: 0.60-0.89]). There were no significant differences in the infection risk between other opioids and morphine.
- CONCLUSION: The risk of serious infections among long-acting opioid users varies by opioid type. Providers should carefully consider the risk of serious infections when making pain management decisions.

Long-acting Opioid Use and the Risk of Serious Infections: A Retrospective Cohort Study. Wiese AD, Griffin MR, Schaffner W, Stein CM, Greevy RA, Mitchel EF, Grijalva CG SOClin Infect Dis. 2019;68(11):1862

# Opiate-Induced Immunosuppression in Infections, Variable Effects

Of 1233 case patients with laboratory-confirmed pneumococcal disease, opioid use was measured based on pharmacy prescription records. **Individuals with invasive pneumococcal disease had greater odds than controls of being current opioid users. Associations were strongest for long-acting opioids** (aOR 1.87, 95% CI 1.24-2.82), **high-potency opioids** (morphine, codeine, oxycodone, hydromorphone, fentanyl), and **higher opioid doses** (especially ≥90 morphine milligram equivalents per day).

Opioid Analgesic Use and Risk for Invasive Pneumococcal Diseases: A Nested Case-Control Study. Wiese AD, Griffin MR, Schaffner W, Stein CM, Greevy RA, Mitchel EF Jr, Grijalva CG SOAnn Intern Med. 2018;168(6):396. Epub 2018 Feb 13.

# Opiate-Induced Immunosuppression, Cancer

Opioids have many non-analgesic effects, including direct and indirect effects on cancer cells and on anti-tumour immunity (NK cells, macrophages and T-cells).

Direct effects on immune cells are manifested via opioid and non-opioid toll-like receptors

Indirect effects are manifested via the sympathetic nervous system and hypothalamic-pituitary-adrenal axis.

Opioids can also decrease/alter immune cell infiltration into the tumour micro-environment.

Animal models have shown that this is not a class effect, in that morphine and fentanyl suppress NK cell cytotoxicity; buprenorphine does not affect NK cell cytotoxicity, whereas tramadol increases NK cell cytotoxicity, reducing metastasis. In healthy individuals, morphine suppresses and fentanyl enhances NK cell cytotoxicity.

Boland JW, Pockley AG. Influence of opioids on immune function in patients with cancer pain: from bench to bedside. *Br J Pharmacol*. 2018;175(14):2726-2736. doi:10.1111/bph.13903

# Opiate-Induced Immunosuppression, Cancer

- Findings: Opiate use was significantly associated with bladder (β = 0.59), kidney (β = 0.16), oral cavity (β = 0.27), esophagus (β = 0.33), larynx (β = 0.17) and other pharynx (β = 0.36) cancers.
- Conclusion: There was a significant association between opiate use and risk of cancers.

AMARashidian H, Zendehdel K, Kamangar F, Malekzadeh R, Haghdoost AA. An Ecological Study of the Association between Opiate Use and Incidence of Cancers. *Addict Health*. 2016;8(4):252-260

# Opiate-Induced Immunosuppression, Cancer

In the present report we show that opioids increase the migratory activity of bladder cancer cells

Indeed, in these cell lines, opioids increase migration, adhesion, spreading and invasion by re-arranging actin cytoskeleton, increasing MMP-2 and -9 secretion and triggering specific intracellular signaling cascades in a non-opioid receptor mediated manner. An interaction, albeit with low affinity, of opioids with the bradykinin B2 receptor is reported, resulting in the increase of migration, while B2 antagonists revert this action.

Vassou D, Notas G, Hatzoglou A, Castanas E, Kampa M. Opioids increase bladder cancer cell migration via bradykinin B2 receptors. *Int J Oncol*. 2011;39(3):697-707. doi:10.3892/ijo.2011.1063

# Opiate-Induced Immunosuppression, Delayed Wound Healing

- Our results show that morphine treatment resulted in a significant decrease in inflammation induced angiogenesis. Taken together, our studies show that morphine regulates the wound repair process on multiple levels. Morphine acts both directly and indirectly in suppressing angiogenesis.

Martin JL, Charboneau R, Barke RA, Roy S. Chronic morphine treatment inhibits LPS-induced angiogenesis: implications in wound healing. *Cell Immunol*. 2010;265(2):139-145. doi:10.1016/j.cellimm.2010.08.002

# Opiate Induced Hyperalgesia

- Definition
- Etiology
- Presentation
- Management

# Opioid-Induced Hyperalgesia, Definition

Opioid-induced hyperalgesia is most broadly defined as a state of nociceptive sensitization caused by exposure to opioids. The state is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain may actually become more sensitive to certain painful stimuli. The type of pain experienced may or may not be different from the original underlying painful condition. Although the precise molecular mechanism is not yet understood, it is generally thought to result from neuroplastic changes in the peripheral and central nervous systems that lead to sensitization of pronociceptive pathways.

Clinicians should suspect expression of hyperalgesia when opioid treatment effect seems to wane in the absence of disease progression, particularly if found in the context of unexplained pain reports or diffuse allodynia unassociated with the pain as previously observed.

Chu LF, Angst MS, Clark D Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. Clin J Pain. 2008;24(6):479

# Opioid-Induced Hyperalgesia, Theories of Etiology

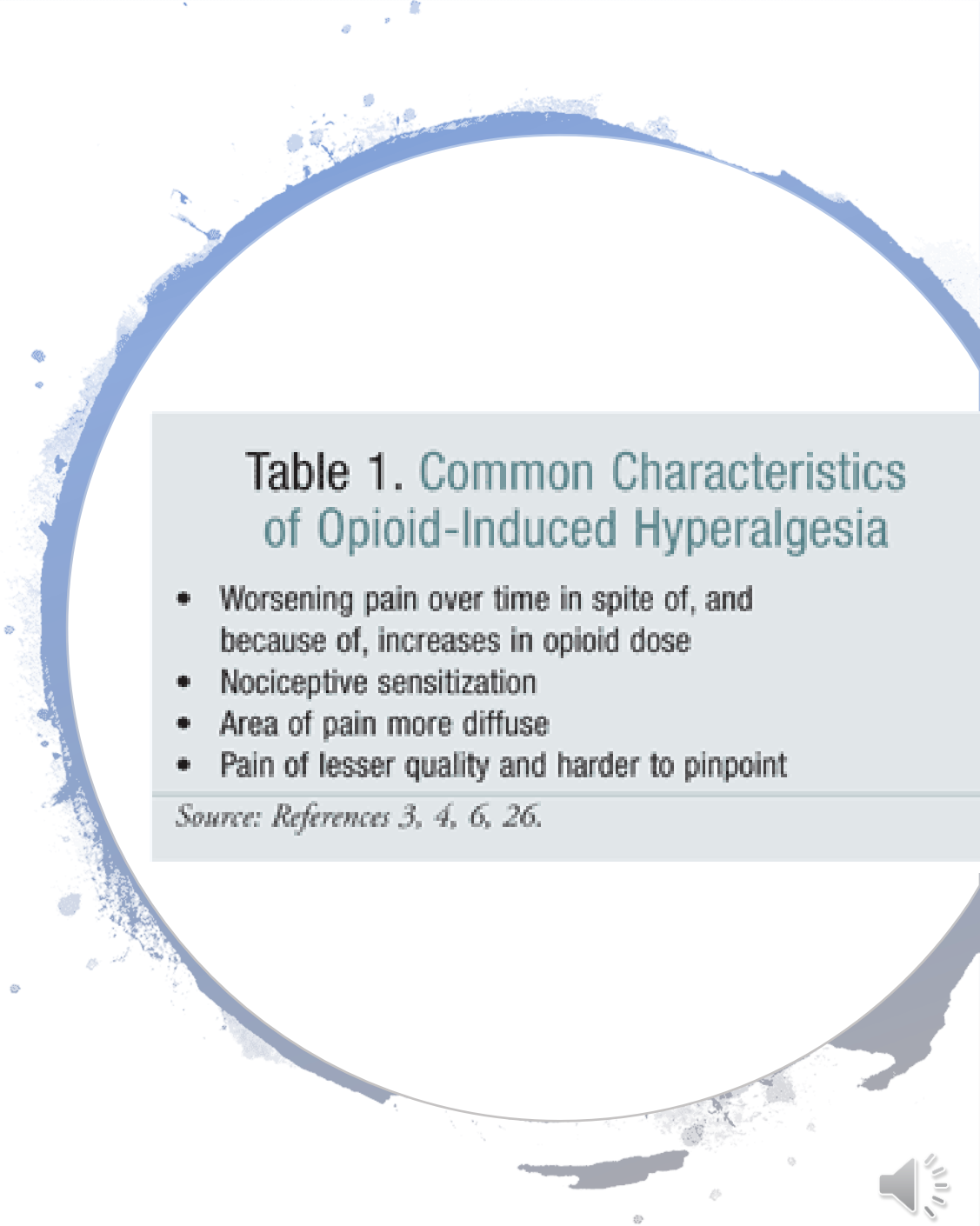
**Neuroexcitatory Model**: the theory that OIH is caused by activity of receptors besides the mu opioid receptor

- evidence that OIH is not alleviated by administration of an opioid antagonist (e.g., naloxone).
- NMDA: certain opioids and their metabolites agonize the *N*-methyl-D-aspartate (NMDA) receptor. Activation of the NMDA receptor causes an influx of calcium that greatly enhances the excitability of the neuron. When the NMDA receptor and corresponding neurons are more active, they can more readily transmit painful impulses initiated by circulating substance P or other noxious stimuli. Some studies show relief of OIH after administration of NMDA receptor antagonists.
- Dynorphin: an endogenous opioid peptide that binds primarily to the kappa opioid receptor and, to a lesser extent, the mu opioid and NMDA receptors. It is believed that dynorphin's agonism of the kappa opioid receptor has a role in the pronociception of OIH despite the presence of pure mu receptor agonists. Studies have shown that reversal of dynorphin can restore the analgesic effects of morphine when subjects are given a dynorphin antiserum. Dynorphin is known to increase during prolonged opioid administration. Dynorphin also causes the release of excitatory neuropeptides within different locations in the central nervous system.

https://www.uspharmacist.com/article/opioid-induced-hyperalgesia-an-emerging-treatment-challenge
*S Pharm.* 2012;37(5):HS-2-HS-7.

# Opioid-Induced Hyperalgesia, Diagnosis and Presentation

- Opioid induced hyperalgesia can  be confused with opioid tolerance.
    - Tolerance can be overcome by increasing the opioid dose, whereas the same increase in a patient with hyperalgesia results in worsened pain.
    - Hyperalgesia differs from tolerance in that the pain intensity is stronger than initially reported.
- Undertreated pain is another possibility. If opioid therapy is suboptimal, increasing the dose should lead to pain relief; if hyperalgesia is present, the opposite should be true.
- Opioid withdrawal can complicate presentation and treatment.
    - As such, pain resolution from opioid discontinuation in hyperalgesia will not be immediate and will require patience.
- OIH tends to present with other distinct characteristics (See hyperalgesia)




https://www.uspharmacist.com/article/opioid-induced-hyperalgesia-an-emerging-treatment-challenge
*S Pharm.* 2012;37(5):HS-2-HS-7.

# Opioid-Induced Hyperalgesia, Treatment Options

- Discontinue the offending opioid.
  - some report that hyperalgesia may likely worsen early in the discontinuation process.
- Some may obtain relief by reducing the opioid dose.
- Switch from one structural class of opioids to another.
  - *Remember to reduce MME for lack of cross tolerance*
  - Studies to date have demonstrated that OIH is more strongly associated with opioids from the phenanthrene class (TABLE 2).

Table 2. Classes of Opioids

| Phenanthrene Opioids | Nonphenanthrene Opioids |
|---|---|
| Codeine | Piperidine derivatives: |
| Hydrocodone | Fentanyl |
| Hydromorphone | Meperidine |
| Morphine | Sufentanil |
| Oxycodone | Other: |
| Oxymorphone | Buprenorphine |
| | Methadone |
| | Tramadol |

*Source: References 11, 14.*

https://www.uspharmacist.com/article/opioid-induced-hyperalgesia-an-emerging-treatment-challenge
*S Pharm.* 2012;37(5):HS-2-HS-7

# Opioid-Induced Hyperalgesia, Other Treatment Approaches

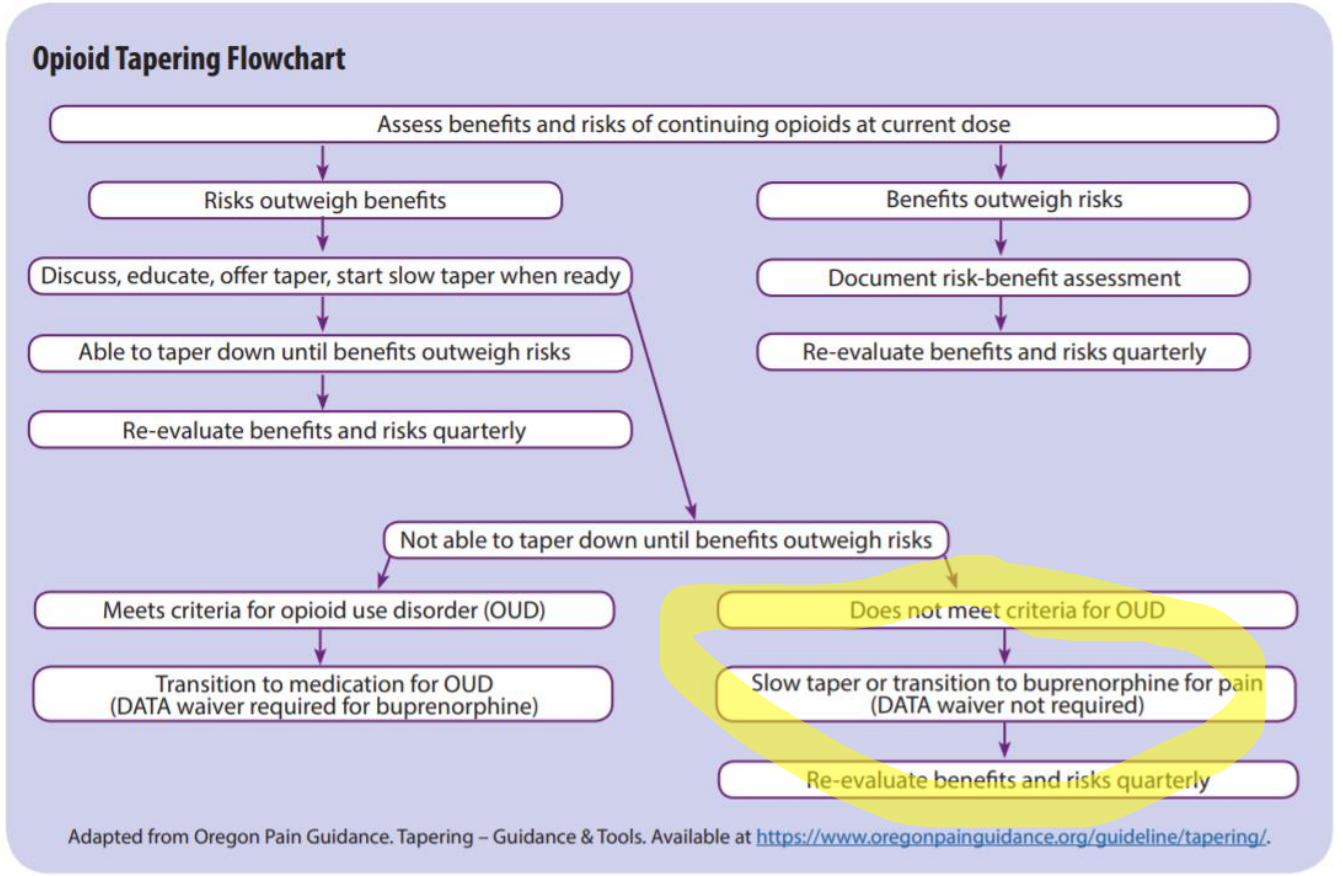
- **Supplement opioid therapy with a cyclo-oxygenase 2 (COX-2) inhibitor:** By reducing prostaglandin synthesis, COX-2 inhibitors can decrease the sensitization of pronociceptive neurons. Nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors appear to have analgesic effects independent of their ability to suppress prostaglandin synthesis peripherally. COX-2 inhibitors also have demonstrated the ability to antagonize the NMDA receptor. Centrally, NSAIDs are capable of antagonizing the NMDA receptor by blocking glutamate, substance P, and other excitatory amino acids. Independent of this, NMDA receptor activation can upregulate COX-2 expression.
- **Antagonize the NMDA receptor:**
  - **Ketamine** has been much researched, but its adverse effects can be severe. While it antagonizes NMDA and provides an anesthetic effect that would promote analgesia, side effects are common, diverse, and severe. These effects include tachyarrhythmia, hypertension, cognitive impairments, and psychomimetic reactions, including mood changes, vivid dreams, delirium, hallucinations, and sedation.
  - **Dextromethorphan** is another NMDA receptor antagonist that has been investigated for the treatment of hyperalgesia. However, studies failed to demonstrate efficacy.
  - **Methadone:** In addition to its analgesic effects through binding to the mu opioid receptor, methadone is a weak NMDA receptor antagonist. It has been reported that the addition of even a low dose of methadone has been effective for reducing hyperalgesia.
  - **Tramadol** and **meperidine** also have some NMDA receptor antagonist activity.

https://www.uspharmacist.com/article/opioid-induced-hyperalgesia-an-emerging-treatment-challenge
*S Pharm.* 2012;37(5):HS-2-HS-7.

# Classic Opiate Alternatives

- Physical Therapy
- Cognitive Behavioral Therapy
- Acupuncture
- Interdisciplinary programs
- Gentle motion
- Biofeedback
- Trigger Points
- Body work
- Procedural Interventions
- Other complementary treatments and therapies
- Weaning/Tapering
- Buprenorphine

# HHS Opiate Tapering Guidelines




https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf
(Adapted from Oregon Pain Guidance. Tapering – Guidance & Tools. Available at https://www.oregonpainguidance.org/guideline/tapering/)

# Buprenorphine for Pain

- If patients on high opioid dosages are unable to taper despite worsening pain and/or function with opioids, whether or not opioid use disorder criteria are met, consider transitioning to buprenorphine.[4,12] Buprenorphine is a partial opioid agonist that can treat pain as well as opioid use disorder,[19] and has other properties that may be helpful,[3] including less opioid-induced hyperalgesia[12] and easier withdrawal than full mu-agonist opioids,[3] and less respiratory depression than other long-acting opioids.[20] Buprenorphine can then be continued or tapered gradually.[12] Transitioning from full-agonist opioids requires attention to timing of the initial buprenorphine dose to avoid precipitating withdrawal.[xi]

Consultation with a clinician experienced in use of buprenorphine is warranted if unfamiliar with its initiation. SAMHSA's Providers Clinical Support System offers training and technical assistance as well as mentors to assist those who need to taper opioids and may have additional questions.

https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf

# Buprenorphine for pain doesn't req DATA waiver

- Neither the Controlled Substances Act, as amended by DATA 2000, nor Drug Enforcement Administration (DEA) regulations Administering or Dispensing Narcotic Drugs, 21 Code of Federal Regulations (CFR) 1306.07 impose any limitations on a physician or other authorized hospital staff to maintain or detoxify a person with buprenorphine as an incidental adjunct to medical or surgical conditions other than opioid dependency.

https://www.samhsa.gov/medication-assisted-treatment/legislation-regulations-guidelines/special

# Buprenorphine

Buprenorphine is a partial mu agonist in the opiate family. The danger of respiratory depression and over-dose related death associated with opiate use is conferred by the mu receptor, making partial mu agonist opiates significantly safer than full mu agonist opiates.


Lutfy K, Cowan A. Buprenorphine: A Unique Drug with Complex Pharmacology. Curr Neuropharmacol [Internet]. 2004 Oct [cited 2020 May 15];2(4):395–402. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2581407/

Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth [Internet]. 2006 May 1 [cited 2020 May 15];96(5):627–32. Available from: https://academic.oup.com/bja/article/96/5/627/313315

Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clin Pharmacol Ther. 1994 May;55(5):569–80.

# Buprenorphine: Limited Respiratory Depression

- BACKGROUND: We measured the effect of two weight adjusted i.v. doses (0.2 mg per 70 kg and 0.4 mg per 70 kg) of the potent opioid buprenorphine on analgesia and respiratory depression in healthy volunteers. The aim of the study was to compare buprenorphine's behaviour with respect to the occurrence of ceiling (or apparent maximum) in these typical micro-opioid protein-(MOP) receptor effects.
- CONCLUSIONS: While buprenorphine's analgesic effect increased significantly, respiratory depression was similar in magnitude and timing for the two doses tested. **We conclude that over the dose range tested buprenorphine displays ceiling in respiratory effect but none in analgesic effect.**

Dahan A, Yassen A, Romberg R, Sarton E, Teppema L, Olofsen E, Danhof M Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627. Epub 2006 Mar 17.

# CDC: Buprenorphine MME

## 2018 CDC MME Chart

**Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors[i,ii]**

| Type of Opioid (strength units) | MME Conversion Factor |
|---|---|
| Buprenorphine film/tablet[iii] (mg) | |
| Buprenorphine patch[iii] (mcg/hr) | |
| Buprenorphine film [iii] (mcg) | |
| Butorphanol (mg) | 7 |
| Codeine (mg) | 0.15 |
| Dihydrocodeine (mg) | 0.25 |
| Fentanyl buccal or SL tablets, or lozenge/troche[iv] | 0.13 |
| Hydrocodone (mg) | 1 |
| Hydromorphone (mg) | 4 |

*iii Buprenorphine products are listed but do not have an associated MME conversion factor. These buprenorphine products, as partial opioid agonists, are not expected to be associated with overdose risk in the same dose-dependent manner as doses for full agonist opioids.*

# Buprenorphine for Pain

- **Partial agonism at the μ-opioid receptor does not provide partial analgesia, but rather analgesia equivalent to that of full μ-opioid receptor agonists**.
- In addition, unlike full μ-opioid receptor agonists, buprenorphine may have a unique role in mediating analgesic signaling at spinal opioid receptors while having less of an effect on brain receptors, **potentially limiting classic opioid-related adverse events such as euphoria, addiction, or respiratory depression.**
- The pharmacokinetic properties of buprenorphine are also advantageous in a clinical setting, where metabolic and excretory pathways allow for use in patients requiring concomitant medications, the elderly, and those with renal or hepatic impairment.
- The unique pharmacodynamic and pharmacokinetic properties of buprenorphine translate to an effective analgesic with a potentially favorable safety profile compared with that of full μ-opioid receptor agonists for the treatment of chronic pain.

Gudin J, Fudin J A Narrative Pharmacological Review of Buprenorphine: A Unique Opioid for the Treatment of Chronic Pain. Pain Ther. 2020;9(1):41. Epub 2020 Jan 28

# Buprenorphine for Pain

RECENT FINDINGS: Buprenorphine is an effective and safe analgesic that is tolerated at least as well, if not better, than other opioids. Given its safety and mechanistic advantages, the authors believe there is an important role for buprenorphine in the treatment of chronic pain severe enough to warrant the use of an opioid analgesic. …advantages of the molecule make it the preferential first-line opioid for around-the-clock pain in our practice.

Fishman MA, Kim PS. Buprenorphine for Chronic Pain: a Systemic Review. Curr Pain Headache Rep. 2018;22(12):83. Epub 2018 Oct 5.

# Buprenorphine & Endocrine Effects

- Following buprenorphine, serum levels of corticosterone and luteinizing hormone were not changed
- Growth hormone release was stimulated in a dose-dependent manner.
- Prolactin release was stimulated after the lowest dose of buprenorphine while the highest dose induced a fall in serum prolactin.
- Similar biphasic effects on thyroid stimulating hormone were seen after buprenorphine.

Pechnick RN, George R, Poland RE. The effects of the acute administration of buprenorphine hydrochloride on the release of anterior pituitary hormones in the rat: evidence for the involvement of multiple opiate receptors. *Life Sci*. 1985;37(20):1861-1868. doi:10.1016/0024-3205(85)90002-5

# Buprenorphine & Endocrine Effects, Eugonadism

We assayed testosterone, free testosterone, estradiol, SHBG, LH, FSH, and prolactin in 17 men treated with buprenorphine. Thirty-seven men treated with high-dose methadone and 51 healthy blood donors served as controls. Sexual function and depression were assessed using a self-rating sexual function questionnaire and the Beck Depression Inventory. Patients treated with buprenorphine had a significantly higher testosterone level [5.1 +/- 1.2 ng/ml (17.7 +/- 4.2 nmol/liter) vs. 2.8 +/- 1.2 ng/ml (9.7 +/- 4.2 nmol/liter); $P < 0.0001$] and a significantly lower frequency of sexual dysfunction ($P < 0.0001$) compared with patients treated with methadone. The testosterone level of buprenorphine-treated patients did not differ from that of healthy controls. **In conclusion, we demonstrated for the first time that buprenorphine, in contrast with high-dose methadone, seems not to suppress plasma testosterone** in heroin-addicted men. To this effect, buprenorphine was less frequently related to sexual side effects. Buprenorphine might therefore be favored in the treatment of opioid dependence to prevent patients from the clinical consequences of methadone-induced hypogonadism.

Bliesener N, Albrecht S, Schwager A, Weckbecker K, Lichtermann D, Klingmüller D. Plasma testosterone and sexual function in men receiving buprenorphine maintenance for opioid dependence. *J Clin Endocrinol Metab*. 2005;90(1):203-206. doi:10.1210/jc.2004-0929

# Buprenorphine & Endocrine Effects, Eugonadism

- Men on MMT, but not BMT, have high prevalence of ED, related to hypogonadism and depression.
- Methadone-treated men had lower TT than buprenorphine-treated men and reference groups; Prolactin did not differ between methadone, buprenorphine groups, and reference groups
- Prevalence of sexual dysfunction was higher among the users of methadone compared with buprenorphine. Patients with sexual difficulty while on methadone treatment were advised to switch to buprenorphine.
- In men being treated for opioid dependence, methadone, but not buprenorphine, is associated with low serum testosterone concentrations and sexual dysfunction.

Hallinan R, Byrne A, Agho K, McMahon C, Tynan P, Attia J. Erectile dysfunction in men receiving methadone and buprenorphine maintenance treatment. *J Sex Med*. 2008;5(3):684-692. doi:10.1111/j.1743-6109.2007.00702.x

Hallinan R, Byrne A, Agho K, McMahon CG, Tynan P, Attia J. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. *Int J Androl*. 2009;32(2):131-139. doi:10.1111/j.1365-2605.2007.00824.x

Yee A, Loh HS, Hisham Hashim HM, Ng CG. The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study. *J Sex Med*. 2014;11(1):22-32. doi:10.1111/jsm.12352

Hypogonadism in patients treated with intrathecal morphine.AUFinch PM, Roberts LJ, Price L, Hadlow NC, Pullan PT SOClin J Pain. 2000;16(3):251. OBJECTIVEThe objective of this study was to investigate the hypothalamic-pituitary-gonadal response to intrathecal opioids.

# Buprenorphine and Immunocompetency

- We analyze the effect of fentanyl and buprenorphine on splenic cellular immune responses in the mouse.
- **No immune alterations were ever present in buprenorphine-treated animals.**
- These results indicate that fentanyl and buprenorphine exert different immune effects.

Martucci C, Panerai AE, Sacerdote P. Chronic fentanyl or buprenorphine infusion in the mouse: similar analgesic profile but different effects on immune responses. *Pain*. 2004;110(1-2):385-392. doi:10.1016/j.pain.2004.04.020

# Buprenorphine and Immunocompetency

- Acute intracerebroventricular administration of buprenorphine has been shown in rats not to affect cellular immune responses, while a statistically significant inhibition of the immune response was observed with morphine.
- In mouse studies, chronic administration of buprenorphine led to immune parameters important for antimicrobial responses or for anti-tumour surveillance (lymphoproliferation, natural killer (NK)-lymphocyte activity, cytokine production, lymphocyte number) being unaffected. In contrast, levels of these immune markers were significantly reduced when the potent micro-agonist fentanyl was administered, but recovered after longer periods as tolerance developed.
- Treating animals immediately after surgery with equianalgesic doses of morphine and buprenorphine significantly reduced surgery-induced immunosuppression.
- **Overall, from several animal studies it emerges that buprenorphine has the more favourable profile, being a potent analgesic devoid of intrinsic immunosuppressive activity**.

Sacerdote P. Opioids and the immune system. *Palliat Med*. 2006;20 Suppl 1:s9-s15.

# Buprenorphine & Hyperalgesia

- In human subjects, buprenorphine exerts an antihyperalgesic effect.
- Buprenorphine has been shown to reverse hyperalgesia induced by opioids through “buprenorphine-induced antinociception.”
- Buprenorphine is a κ-receptor antagonist and can compete with the effect of spinal dynorphin, an endogenous κ-receptor agonist. Because spinal dynorphin is increased after opioid exposure and contributes to hyperalgesia, this competitive effect of buprenorphine on the κ-receptor binding site may decrease the effect of spinal dynorphin resulting in the decreased hyperalgesia.
- Buprenorphine showed an enhanced ability to treat hyperalgesia experimentally induced in volunteers compared to fentanyl.

Koppert, W, Ihmsen, H, Körber, N, Wehrfritz, A, Sittl, R, Schmelz, M, Schüttler, J Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model.. *Pain*. (2005). *118* 15–22 [Article]

Lutfy, K, Eitan, S, Bryant, CD, Yang, YC, Saliminejad, N, Walwyn, W, Kieffer, BL, Takeshima, H, Carroll, FI, Maidment, NT, Evans, CJ Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors.. *J Neurosci*. (2003). *23* 10331–7

Gardell, LR, Wang, R, Burgess, SE, Ossipov, MH, Vanderah, TW, Malan, TPJr, Lai, J, Porreca, F Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release from primary afferent fibers.. *J Neurosci*. (2002). *22* 6747–55

Lee, M, Silverman, SM, Hansen, H, Patel, VB, Manchikanti, L A comprehensive review of opioid-induced hyperalgesia.. *Pain Physician*. (2011). *14* 145–61

# Preference for Buprenorphine in Elderly

Taking into consideration all the very limited available evidence from preclinical and clinical work, buprenorphine can be recommended, while morphine and fentanyl cannot.

- For all opioids except buprenorphine, half-life of the active drug and metabolites is increased in the elderly and in patients with renal dysfunction. It is, therefore, recommended that--except for buprenorphine--doses be reduced, a longer time interval be used between doses, and creatinine clearance be monitored. Thus, buprenorphine appears to be the top-line choice for opioid treatment in the elderly.
- Buprenorphine is the only opioid demonstrating a ceiling for respiratory depression when used without other CNS depressants.
- Age is related to a gradual decline in the immune system: immunosenescence, which is associated with increased morbidity and mortality from infectious diseases, autoimmune diseases, and cancer, and decreased efficacy of immunotherapy, such as vaccination.

Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008;8(4):287-313. doi:10.1111/j.1533-2500.2008.00204.x

# Buprenorphine and Prolonged QTc

- Butrans dose of 40 mcg/hour (given as two Butrans 20 mcg/hour Transdermal Systems) was observed to prolong the QTc interval.
- Consider these observations in clinical decisions when prescribing Butrans to patients with hypokalemia or clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia.
- Avoid the use of Butrans in patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (e.g., sotalol, amiodarone, dofetilide), or other medications that prolong the QTc interval.

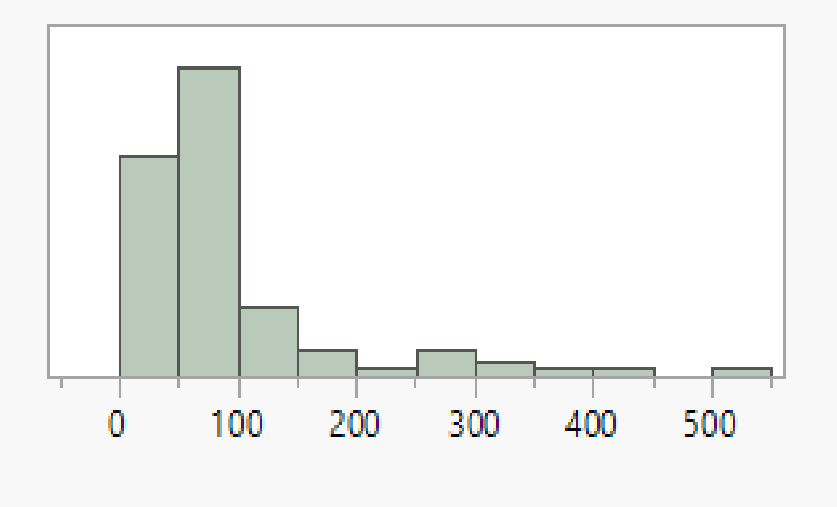
# Buprenorphine and Prolonged QTc

- **Conclusion** Buprenorphine is associated with less QTc prolongation than levomethadyl or methadone and may be a safe alternative.

Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MCP. QT-Interval Effects of Methadone, Levomethadyl, and Buprenorphine in a Randomized Trial. *Arch Intern Med.* 2007;167(22):2469–2475. doi:10.1001/archinte.167.22.2469

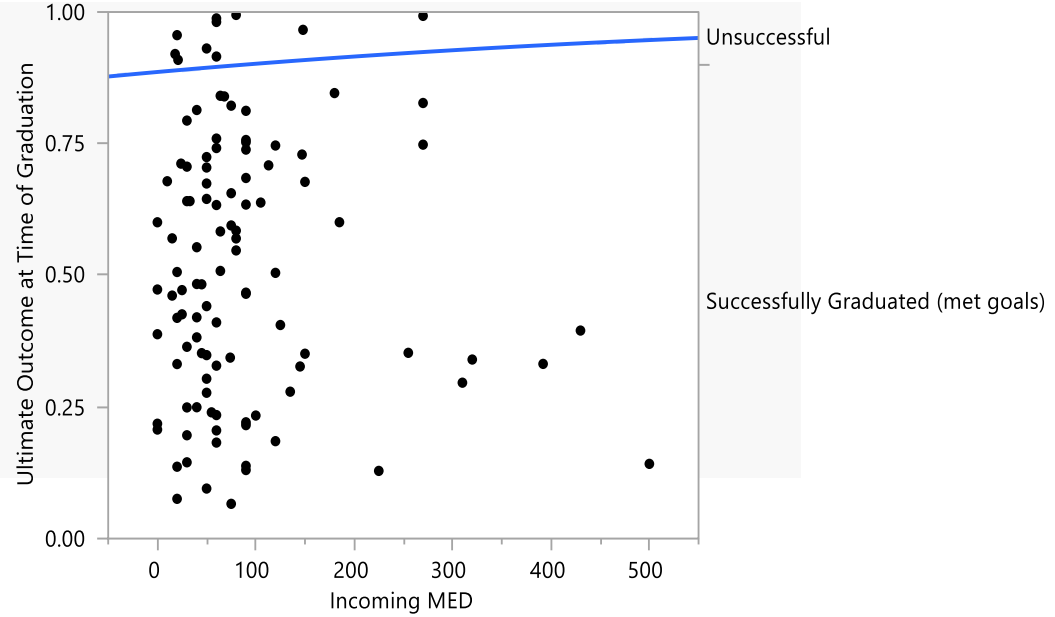
# The FOOT Steps Study
# (Focus on Opiate Transitions)

**Incoming MME of FOOT Steps participants**



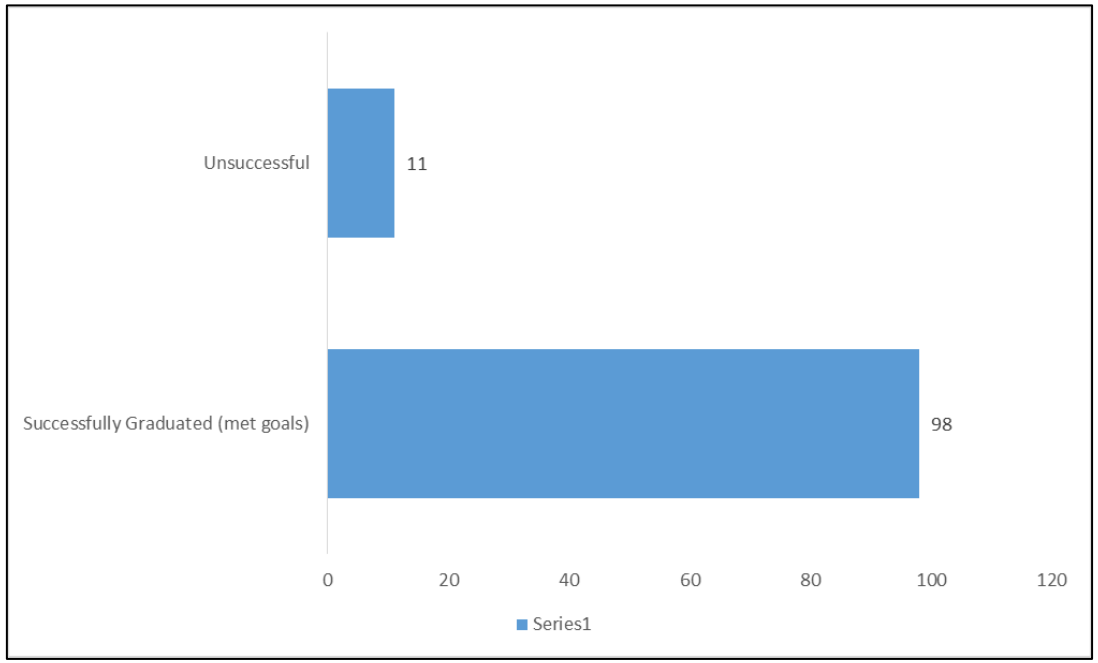

**Logistic Fit of Ultimate Outcome at Time of Graduation By Incoming MME**

***(Success was NOT dependent upon incoming MME amount.***



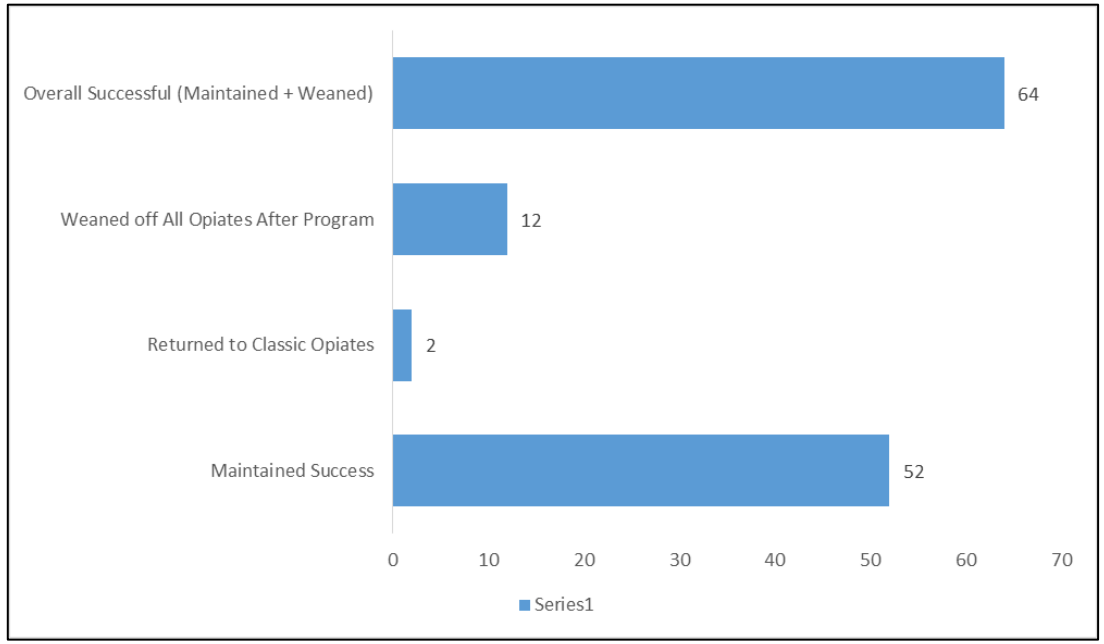
# FOOT Steps Outcomes

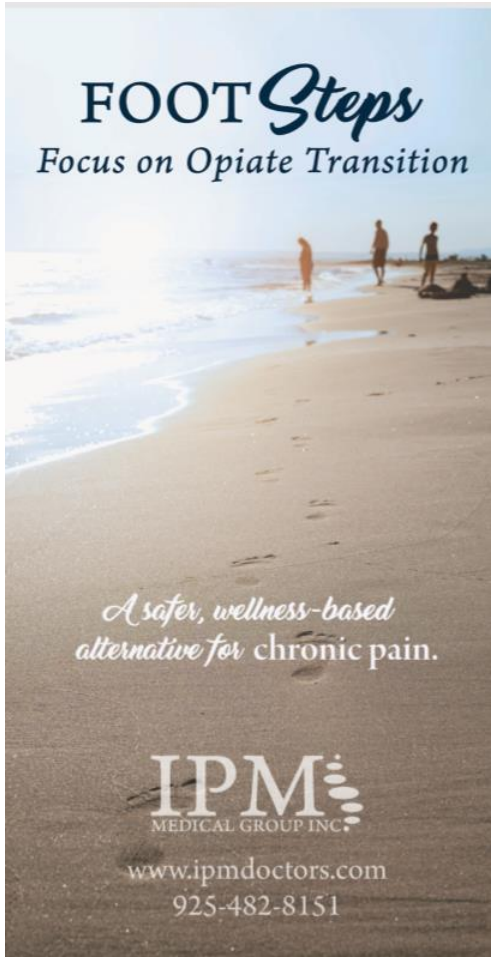
**Successful rate of graduation from FOOT Steps: 90%**




**Extended follow up outcomes (up to 24 months of follow up):**

**97% classic opiate abstinence maintained!**






## Participants Say....

*"You'll get your life back." GL*

*"The treatment team could not have been more compassionate and made my transition seamless." JD*

*"Try this program with an open mind. This program does help. It helped me." MG*

*"Best program ever taken!" RS*

*"No need to face this alone - the support and knowledge gained from the group is a comfort." CT*

# Complications of Long-Term Opiate Use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