



INTRODUCTION

- An estimated 5% of Americans have a chronic opioid prescription
- While many side effects of chronic opioids are well studied and reported, opioid-induced adrenal insufficiency (OIAI) is a serious, but under-recognized sequelae of long-term opioid use
- As electrolyte abnormalities such as hyperkalemia, hyponatremia, and/or hypercalcemia are often the initial presentations of OIAI, a high clinical suspicion must be present for diagnosis

CASE PRESENTATION

- A 61-year-old female with a history of atrial fibrillation (AFib), heart failure with preserved ejection fraction (HFpEF, EF 60%), hypothyroidism, chronic kidney disease (CKD), schizophrenia, and opioid use disorder (OUD) on methadone maintenance therapy (35mg daily) since 2013 was admitted for lower extremity pain and found to have hyperkalemia (7.3 mMol/L) and AKI on CKD.
- Hyperkalemia was refractory to cessation of RAAS inhibitors and heparin and persisted despite resolution of AKI.
- More aggressive management including calcium gluconate was required for cardiac stabilization and potassium binders were initiated for maintenance therapy
- Concurrently, the patient has symptoms of nausea, fatigue, lightheadedness, and was persistently hypoglycemic and hypotensive, prompting suspicion of adrenal insufficiency.

MAKING THE DIAGNOSIS

- Multiple AM cortisol levels were low-normal
- ACTH, DHEA, FSH, and prolactin were borderline low
- Pituitary MRI showed a diminutive gland (2.5mm), normal infundibular stalk, but to other hypo-enhancing or structural abnormalities.
- Patient has not been on glucocorticoids since 2014, and cortisol testing in 2015 was normal.
- Patient was not on any other narcotics

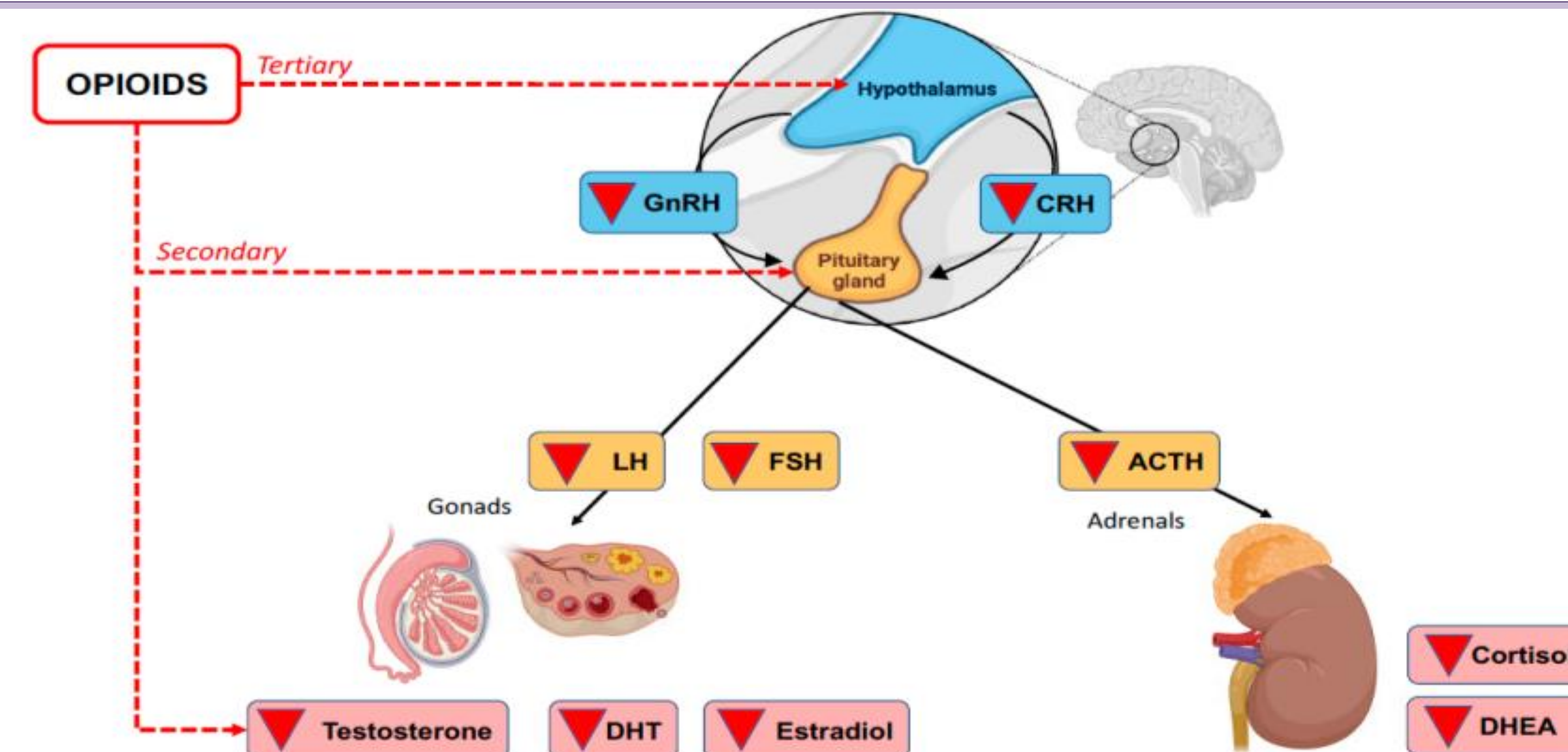


Figure 1. Opioid-induced secondary and tertiary adrenal insufficiency.

Lab	Result	Reference range	Interpretation
AM cortisol	4.5 ug/dL	5.3 - 22.5 ug/dL	Low
ACTH	6 pg/mL	7 - 63 pg/mL	Low
DHEA	14 ng/dL	Postmenopausal (77-851ng/dL)	Low
FSH	28.8 mIU/mL	Post-menopausal: 23.0 - 116.3 mIU/mL	Low-normal
TSH	4.516 uIU/mL	0.550 - 4.780 uIU/mL	normal
Free T4	1.22 ng/dL	0.89 - 1.76 ng/dL	normal
Prolactin	3.8 ng/mL	1.8 - 20.3 ng/mL	Low-normal

Table 1. Endocrine Testing with Interpretation

DISCUSSION & LIETRATURE REVIEW

- While OIAI has been described since at least the 1980s, the pathophysiological mechanism is still not well described
 - Proposed mechanism includes interactions with opioid receptors on the hypothalamus and anterior pituitary, leading to decreases in CRH release, with related downstream endocrine sequela (see Figure 1)
- The incidence of OIAI is currently estimated to be around 9% to 29% of all long-term opioid users, although cases are likely under-reported
- In addition to electrolyte abnormalities, symptoms of OIAI can be nonspecific and include musculoskeletal pain, weight loss, fatigue, gastrointestinal symptoms, and sexual dysfunction
- OIAI is likely a diagnosis of exclusion.
- There is no currently agreed-upon diagnostic criteria for OIAI; workup should include morning cortisol levels and a test of appropriate cortisol response after stimulation. Testing of other pituitary hormone levels may assist in diagnosis, and structural causes as well as other iatrogenic causes should be ruled out.
- Definitive treatment is cessation of all opioids.
 - For patients who have been on a relatively short course, the adrenal insufficiency may be reversible
 - For those who have been on long-term opioid therapy, the adrenal insufficiency is often permanent, and treatment involves lifelong steroid replacement

REFERENCES

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2. Donegan D, Bancos I. Opioid-Induced Adrenal Insufficiency. *Mayo Clinic Proceedings.* 2018;93(7):937-944. doi:[10.1016/j.mayocp.2018.04.010](https://doi.org/10.1016/j.mayocp.2018.04.010)