When Endocrine Abnormalities are a Medication Side Effect

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DISCLOSURES

- Sadly, we have nothing to disclose

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OBJECTIVES

- Identify commonly used drugs that may cause new endocrine abnormalities
- Discuss mechanisms for development of such abnormalities
- Touch on risk factors for the development of some medication induced endocrine abnormalities
- Mention principles to guide work-up and treatment

THYROID AND DRUGS

Amiodarone

- Can cause hyper- or hypothyroidism
- One amiodarone molecule contains two atoms of iodine
- Amiodarone has 75 mg iodine/tablet
- 6 mg released into circulation
- WHO recommendation 150 mcg/day I_2

Amiodarone

- Clinically significant thyroid dysfunction occurs 5-15%
- Risk factors for hypothyroidism:
  - Female
  - Positive thyroid antibody
  - Residence in an iodine-repleted region
- Thyrotoxicosis 2-12%
  - Risk factors: male, iodine deficient region

Amiodarone

- Iodine deficient: **Hyper**thyroid
- Iodine excess: **Hypo**thyroid

Lithium

- Once used as an antithyroid drug
- 1-3% people develop goiter
- May precipitate undiagnosed autoimmune thyroid disorders
- Can block thyroid hormone release from thyroglobulin

PPIs

- Raise gastric pH
- Certain level of stomach acid necessary for ingestion of thyroxine (dissolve pills)
- TSH increased with PPI treatment
- Reduce absorption by reducing dissolution of pills
- Liquid formulation may solve problem

Miscellaneous Drugs

- Thyroid hormone is actively oxidized and conjugated in the liver by cytochrome P450
- Drugs activating this system increase metabolic clearance rate of thyroid hormone
  - Rifampin
  - Phenytoin, carbamazepine
  - Barbiturates
- Only mild thyroid function test abnormalities in normal subject

Iron

- May interfere with absorption of thyroxine
- Should not be taken at the same time

Foods

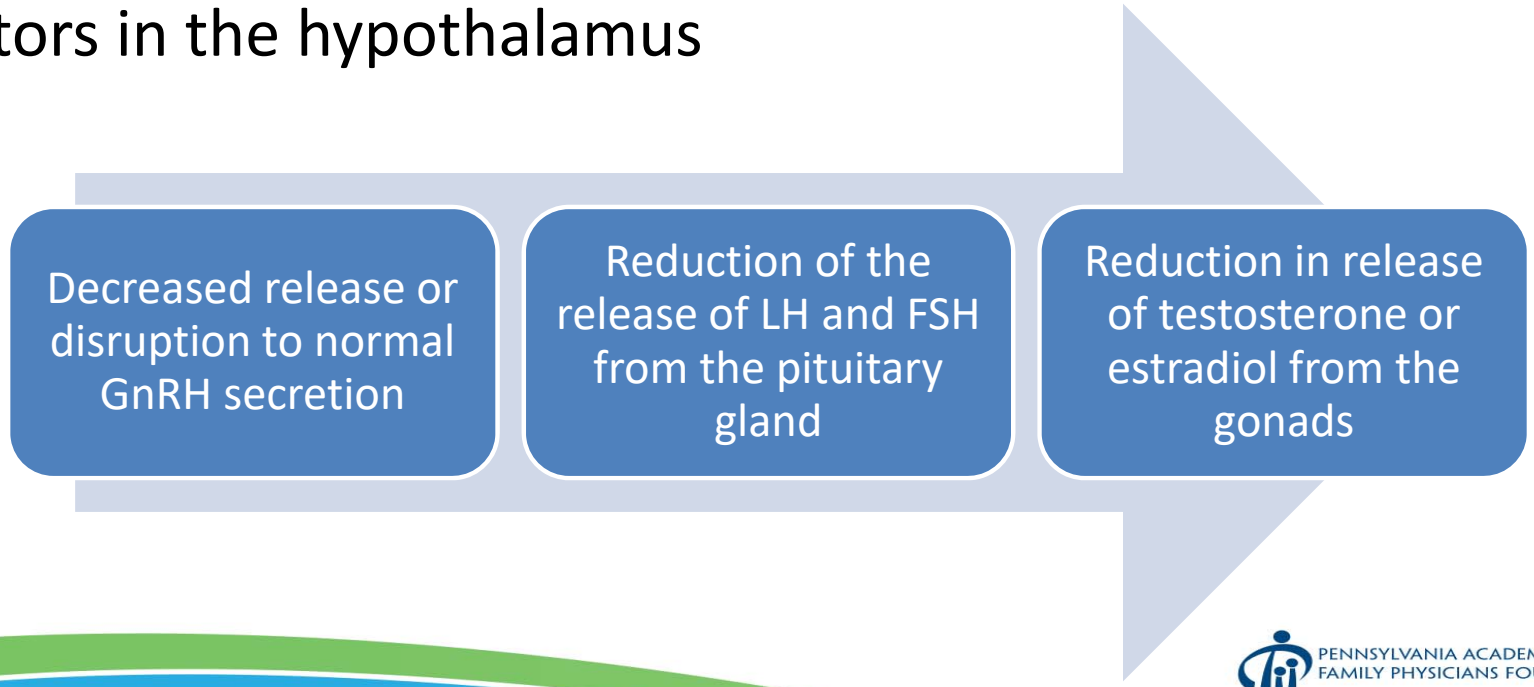
- Decreased absorption Levothyroxine
  - Coffee
  - Soybeans
  - Grapefruit juice (lots)
- Increased absorption
  - Vitamin C

Opioid-Induced Hypogonadism

"[Opium] has kept, and does now keep down the population: The women have fewer children than those of other countries…the feeble opium-smokers of Assam…are more effeminate than women."

– Charles Alexander Bruce, 1839

Opioids modulate gonadal function primarily by acting on opioid receptors in the hypothalamus



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- Opioids may also have direct effects on the pituitary gland and the testes
- Opioids are occasionally reported to increase prolactin levels, which reduces testosterone secretion
- Hyperprolactinemia inhibits the secretion of GnRH

Consequences of Hypogonadism

- Men
  - Erectile dysfunction
  - Impotence
  - Loss of muscle mass and strength
- Women
  - Irregular menstrual periods
  - Oligomenorrhea
  - Amenorrhea
- Both sexes
  - Flushing and sweating
  - Loss of libido
  - Infertility
  - Depression and anxiety
  - Low energy levels
  - Osteoporosis and fractures

- Long-term opioid abuse or use is also a major cause of hypogonadism in women
- Several studies on methadone-maintained men and heroin addicts have demonstrated decreased testosterone levels consistent with central hypogonadism

Atypical Antipsychotic-Induced Hyperglycemia

- Atypical antipsychotics, especially olanzapine and clozapine, have been associated with hyperglycemia
- Mechanisms thought to include:
  - Decreased peripheral insulin sensitivity
  - Decreased insulin secretion
  - Promote weight gain
  - May cause hyperglycemia through drug-induced pancreatitis

Signs and Symptoms of Drug-Induced Hyperglycemia

- Mild-to-moderate disease
- Severe disease

Risk Factors for Drug-Induced Hyperglycemia

- Patients with underlying risk factors for DM2
- Higher doses or misuse of suspected drug
- Use of more than one drug than can induce hyperglycemia
- Drug interactions

Drug-Induced SIADH (Secretion)

- Antipsychotics
- SSRIs
- MAO inhibitors
- Chemotherapeutic agents
- Amiodarone
- Bromocriptine
- Cipro
- Nicotine
- MDMA (ecstasy)

Drug Induced SIADH

- Carbamazepine (increased sensitivity to ADH in renal collecting tubular cells)

- Chlorpropamide (increased ADH receptors in renal collecting tubular cells)

DRUGS CAUSING ADRENAL INSUFFICIENCY

- Megestrol
- Ketoconazole
- Metyrapone
- Aminoglutethimide
- Mitotane
- Glucocorticoid withdrawal (e.g. prednisone, dexamethasone, hydrocortisone)

DRUGS THAT CAUSE GYNECOMASTIA

- Anti-androgens (finasteride, flutamide, spironolactone)
- Anabolic steroids/androgens
- Antiretroviral therapy
- Tricyclic antidepressants
- Digoxin
- Calcium channel blockers
- Metoclopramide
- Prednisone
- Chemotherapeutic agents
- Prolonged ketoconazole

DRUGS THAT CAUSE GYNECOMASTIA

- Cimetidine
- Phenothrin
- First generation antipsychotics
- Omeprazole
- Alcohol
- Amphetamines
- Marijuana
- Heroin, methadone

How to Treat Drug-Induced Gynecomastia

- Usually reversible if < 6-12 months since onset
- Check for other causes (renal, thyroid, hepatic)
- Mammography can confirm, distinguish from pseudogynecomastia
- Stop the offending drug if that appears to be the cause
- Switch to a member of the same class less likely to cause
- Tamoxifen trial for resistant cases or if cannot D/C the drug
- Surgery as last resort
- Note many of these drugs also cause hyperprolactinemia via dopamine receptor blockade

DIAGNOSTIC APPROACH

- Endocrine abnormalities generally diagnosed by checking hormone levels
- Careful drug history with temporal relationship is important
- May need drug withdrawal followed by re-challenge to make dx.
- Drugs may interfere with testing too

Drugs That Affect Diagnostic Tests

- Carbamazepine affects measurement of urine cortisol
- Antidepressants, antipsychotics, levodopa, methyldopa, & labetalol may affect measurement of urine catecholamines
- Isoniazid, phenytoin, & carbamazepine may affect dexamethasone suppression test results

References

Barbesino G. Drugs affecting thyroid function. *Thyroid*. 2010 Jul;20(7):763-70. doi: 10.1089/thy.2010.1635.

Cinemre H, Bilir C, Gokosmanoglu F, Bahcebasi T. Hematologic effects of levothyroxine in iron-deficient subclinical hypothyroid patients: A randomized, double-blind, controlled study. *J Clin Endocrinol Metab*. 2009;94(1):151–156. doi:10.1210/jc.2008-1440

De Maddalena C, Bellini M, Berra M, et al. Opioid-Induced Hypogonadism: Why and How to Treat It. *Pain Physician*. 2012;2012(15):ES111-ES118.

Ma,Ronald et al. Drug-Induced Endocrine & Metabolic Disorders. *Drug Safety.* 2007: 30 (3): 215-245

Roberto, G et al. Drug-induced gynecomastia. *Focus Farmacovigilanza.* 2013; 77 (7): 2

Skelin M, Lucijanić T, Amidžić Klarić D, et al. Factors affecting gastrointestinal absorption of levothyroxine: A review. *Clin Ther*. 2017 Feb;39(2):378-403. doi: 10.1016/j.clinthera.2017.01.005. Epub 2017 Jan 30.

Tisdale JE, Miller DA. Drug-Induced Diseases: Prevention, Detection, and Management. American Society of Health-System Pharmacists; 2010.