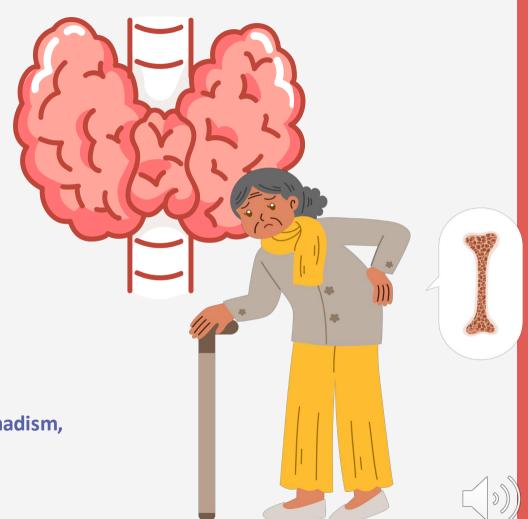
Endocrine System

Pituitary, Thyroid, Parathyroid, Adrenal, Hypogonadism, and Osteoporosis



Learning Objectives

- Describe the mechanism of action and clinical uses of vasopressin and desmopressin, including differences in V1 and V2 receptor activity.
- 2. Explain how dopamine agonists regulate pituitary hormone secretion, particularly their role in treating hyperprolactinemia and acromegaly.
- 3. Identify the therapeutic applications and adverse effects of somatostatin receptor ligands, such as octreotide, in endocrine and GI conditions.
- 4. Compare the pharmacologic properties and clinical indications of levothyroxine and liothyronine, including considerations in special populations.
- 5. Summarize the mechanisms and uses of antithyroid drugs (methimazole and PTU), including their role in hormone synthesis inhibition and peripheral conversion.



Learning Objectives

- 6. Discuss the indications and safety considerations for radioactive iodine therapy in hyperthyroidism and thyroid malignancies.
- 7. Describe the mechanism of action and indications for calcium-sensing receptor mimetics, including cinacalcet in hyperparathyroid conditions.
- 8. Explain the role of bisphosphonates and SERMs in bone metabolism disorders, including mechanisms and long-term monitoring.
- 9. Recognize the clinical use, benefits, and risks of vitamin D and calcium supplementation in metabolic bone disease and deficiency states.
- 10. Outline the indications, actions, and contraindications of sex hormone-related therapies, including testosterone, clomiphene and leuprolide.

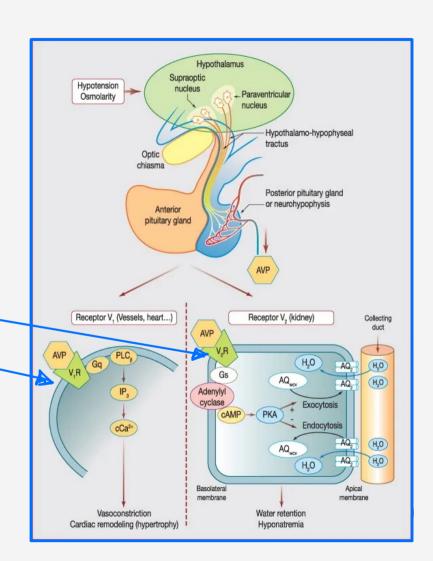
HPA Medications



Vasopressin, Desmopressin Acetate

General

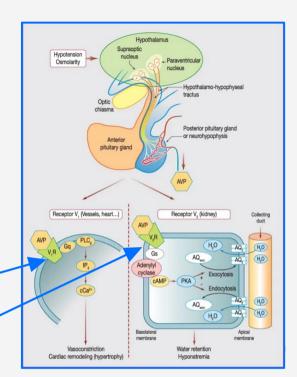
- Vasopressin (ADH)
 - Synthetic vasopressin
 - Agonist effects on V1 and V2
- Desmopressin acetate
 - Analog of vasopressin
 - ∘ V2 >> V1 agonist

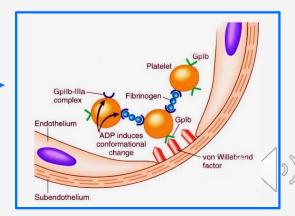


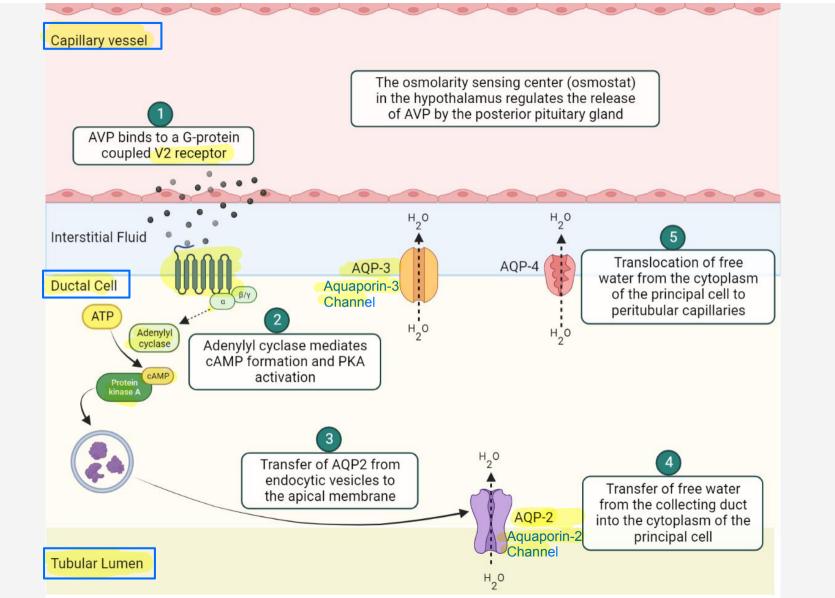
Vasopressin, Desmopressin

Mechanism of Action

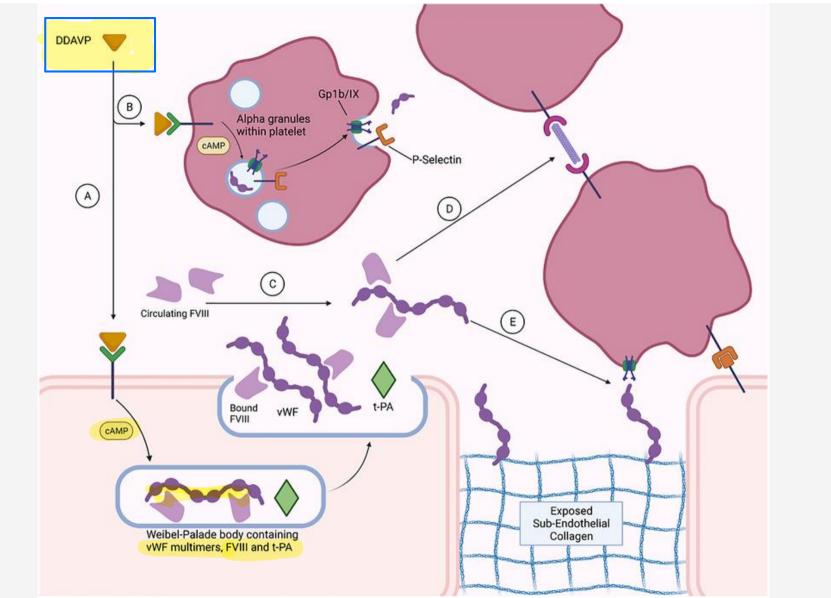
- V1 receptor-mediated effects
 - Gl and vascular smooth muscle contraction
- V2 receptor-mediated effects
 - Water conservation
 - Increases the plasma concentration of von Willebrand factor and factor VIII









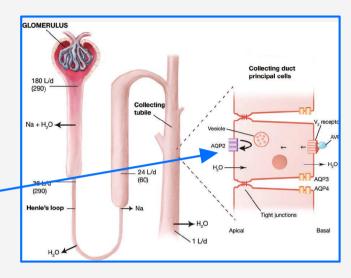


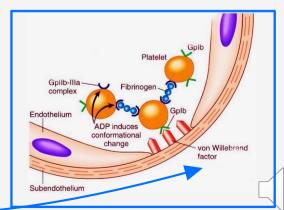
Vasopressin, Desmopressin

Mechanism of Action – Desmopressin

- Activates V2 receptors
 - Inserts aquaporin-2 channels in collecting duct

 - Reduces urine volume in DI
 - Also
 † von Willebrand factor and factor VIII





Vasopressin, Desmopressin

Indications

- V1 receptor agonists (vasopressin)
 - Vasodilatory shock
- V2 receptor agonists (desmopressin)
 - Central DI
 - Acute epistaxis intranasally
 - Von Willebrand Disease type 1
 - Hemophilia A (mild-moderate)
 - Nocturnal enuresis



Vasopressin, Desmopressin

Prescribing Desmopressin (Central DI)

- Solution administered intranasally every 8 24 hours PRN
- Metered dose spray starting at 0.05 0.1 ml every 12– 24 hours
- Other preparations: PO, SL, IV, IM, SC



Vasopressin, Desmopressin

Adverse Effects

- Hyponatremia/ water intoxication
- Conjunctivitis, rhinitis
- Emotional changes, depression, increased risk of suicide

Contraindications

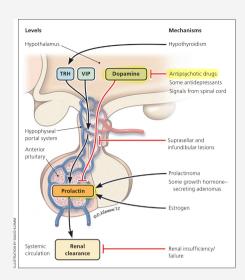
- Hyponatremia or fluid overload
- Moderate or severe renal impairment
- Type IIB von Willebrand disease
- Uncontrolled cardiovascular disease

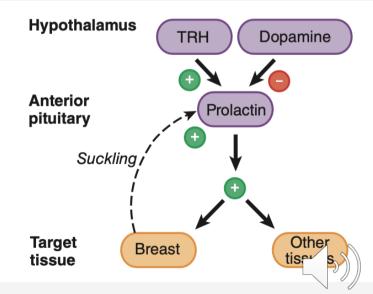


Cabergoline, Bromocriptine, Quinagolide

Mechanism of Action

- Dopamine D2 Receptor agonist at pituitary gland
- Cabergoline has highest D2 affinity
- Bind pituitary D2 receptors
 - \bigcirc \downarrow cAMP in lactotrophs \rightarrow
 - ↓ prolactin (PRL) release
 - Reduces GH secretion





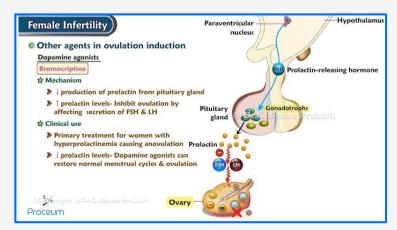
Cabergoline, Bromocriptine, Quinagolide

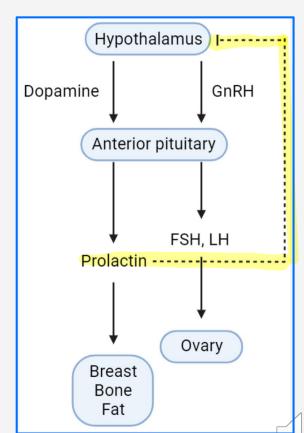
Mechanism of Action

 Low PRL relieves inhibitor effect of hyperprolactinemia on ovulation

Permit patients with prolactinomas to

become pregnant





Cabergoline, Bromocriptine, Quinagolide (not available in US)

Indications

- Acromegaly and hyperprolactinemia/prolactinoma (cabergoline)
- Amenorrhea, galactorrhea, infertility from high prolactin
 - Cabergoline >> bromocriptine (more effective and less side effects)
- Parkinson's disease (bromocriptine)



Cabergoline, Bromocriptine, Quinagolide

Prescribing for Hyperprolactinemia

- Take at bedtime to avoid adverse effects (fatigue, dizziness, orthostatic hypotension)
- Cabergoline
 - 0.25 mg PO weekly
 - Slowly increase

Cabergoline, Bromocriptine, Quinagolide

Adverse Effects

- Fatigue, dizziness, headaches
- Nausea, vomiting
- Orthostatic Hypotension

 Dopamine agonists lower BP primarily by venous and arterial dilation
- Psychiatric disturbance (psychosis, insomnia, depression, impulse control disorder, hypersexuality)
- Valvular heart disease (high Cabergoline)

Contraindications

- Uncontrolled hypertension
- Cardiac valvular disease
- Severe psychiatric illness

Cardiac valvular fibrosis: Ergot alkaloids and derivatives have been associated with fibrotic valve thickening (eg, aortic, mitral, tricuspid); usually associated with long-term, chronic use.

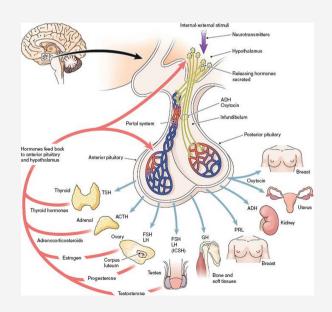


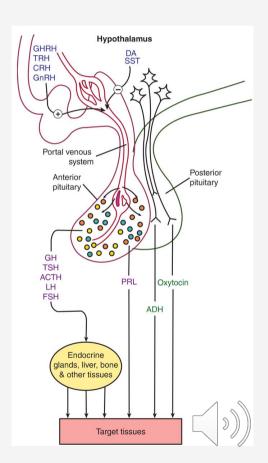
Somatostatin Receptor Ligands

Octreotide

General

Long-acting synthetic analogs of somatostatin





Somatostatin Receptor L

Octreotide

Mechanism of Action

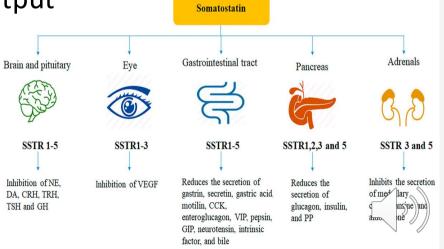
- Binds SSTR2 and SSTR5 receptors
 - ◆ Secretion of GH, TSH, insulin, glucagon
- Inhibits neuroendocrine tumor hormone output
 - Suppresses serotonin, VIP, and gastrin

Octreotide mimics natural somatostatin by inhibiting serotonin release and the secretion of gastrin, VIP, insulin, glucagon, secretin, motilin, and pancreatic polypeptide. Decreases growth hormone (GH) and IGF-1 in acromegaly. Octreotide provides more potent inhibition of GH, glucagon, and insulin as compared to endogenous somatostatin. Also suppresses secretion of thyroid-stimulating hormone and decreases splanchnic blood flow.

Octreotide (somatostatin analogue)

Mechanism of the anti-diarrheal action:

- 1. It inhibits the secretion of many GIT hormones, including gastrin, cholecystokinin, glucagon, insulin, secretin, pancreatic polypeptide, vasoactive intestinal peptide, and 5-HT3.
- 2. It reduces intestinal fluid secretion and pancreatic secretion.
- 3. It slows gastrointestinal motility and inhibits gallbladder contraction.
- 4. It induces direct contraction of vascular smooth muscle, leading to a reduction of portal and splanchnic blood flow.



Somatostatin Receptor Ligands

Octreotide

Indications

- Acromegaly
- Carcinoid syndrome
- Gastrinoma
- Glucagonoma
- Variceal hemorrhage



Somatostatin Receptor Ligands

Octreotide

Adverse Effects

- Nausea, diarrhea, abdominal cramping
- Gallstones
 - Octreotide Inhibits gallbladder contraction
- Bradycardia
- Cardiac conduction abnormalities

Contraindications

- Caution in gallbladder disease
- Bradycardia or arrhythmia



Thyroid Medications



Levothyroxine (T4), Liothyronine (T3)

General

- T4 converted to T3 in target cells, liver, kidneys
- T3 is 10x more potent than T4
- Levothyroxine is hormone of choice for thyroid hormone replacement (due to consistent potency and prolonged duration of action)
- Maximum effect seen after 6-8 weeks of therapy



Levothyroxine (T4), Liothyronine (T3)

Mechanism of Action

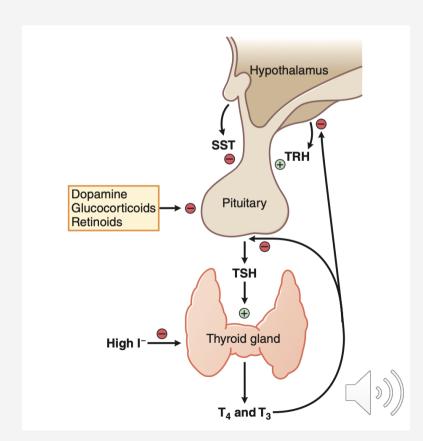
- Activation of nuclear receptors
- Results in gene expression of RNA formulation and protein synthesis



Levothyroxine (T4), Liothyronine (T3)

Indications

- Hypothyroidism
- TSH suppression in thyroid cancer



Levothyroxine (T4), Liothyronine (T3)

Prescribing

- 1.6 mcg/kg body weight, averaging 125 mcg daily
- Check TSH, FT4, and FT3 levels monthly after starting therapy
- Patients should take medication in the morning with water
- Pregnancy requires higher doses



Levothyroxine (T4), Liothyronine (T3)

Adverse Effects

- Atrial fibrillation (in elderly)
- Osteoporosis (in post-menopause)

Contraindications

- Untreated adrenal insufficiency
- Thyrotoxicosis
- thyroid hormones can increase the metabolic clearance of glucocorticoids (i.e., cortisol), leading to an adrenal crisis by exacerbating the underlying insufficiency.

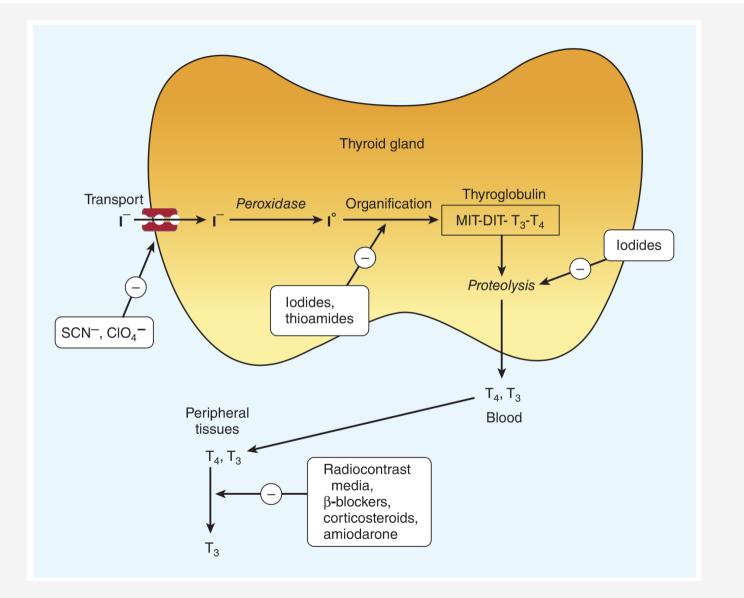


Levothyroxine (T4), Liothyronine (T3)

Interactions

- Drugs/Factors that increase levothyroxine dosage requirements
 - Aluminum hydroxide antacids, PPI, sucralfate
 - Bile acid sequestrants (cholystyramine)
 - Calcium carbonate
 - Iron
 - Fiber
- Impaired T4 to T3 conversion
 - Amiodarone







Propranolol

Propranolol

Mechanism of Action

- Block β1 and β2 receptors
- Inhibits peripheral conversion of T4 to T3 (propranolol only)
- Cardiovascular effects discussed in Cardiovascular Section



Propranolol

Propranolol

Indications

- Thyroid storm
- Symptomatic hyperthyroidism
- Performance anxiety
- Essential tremor



Beta-Blockers

Propranolol

Adverse Effects

- Bradycardia, hypotension
- Fatigue and dizziness
- Bronchospasm
 (especially in asthmatics)
- Cold extremities, depression

Contraindications

- Asthma or COPD
- Bradycardia and heart block
- Hypotension



Methimazole, Propylthiouracil (PTU)

General

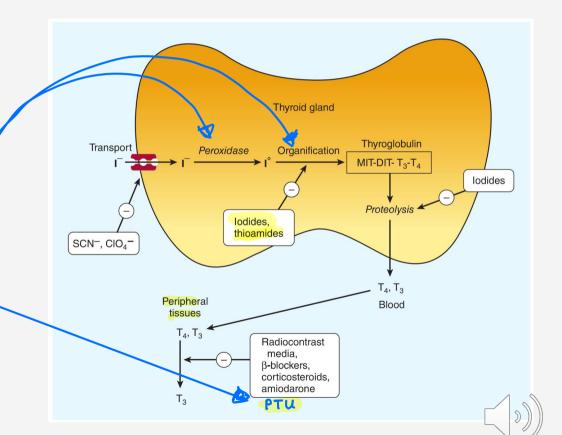
- Methimazole (preferred agent)
 - Not safe during 1st trimester of pregnancy
- Propylthiouracil (PTU)
 - Safer in patients trying to conceive and 1st trimester of pregnancy
 - Preferred in thyroid storm or severe hyperthyroidism



Methimazole, Propylthiouracil (PTU)

Mechanism of Action

- Inhibit thyroid **peroxidase** rxns
- Inhibit iodine organification
- Inhibit **peripheral conversion** of T4 to T3 (PTU only)



Methimazole, Propylthiouracil (PTU)

Mechanism of Action

- Inhibit iodine incorporation into tyrosyl residues on thyroglobulin
- Prevent coupling of iodotyrosyl residues to form T3 and T4
- Act by inhibiting thyroid peroxidase enzyme
- Lead to depletion of iodinated thyroglobulin stores
- PTU also inhibits peripheral T4 to T3 conversion (Methimazole does not)



Methimazole, Propylthiouracil (PTU)

Indications

- Hyperthyroidism (Graves disease)
- Mild Thyrotoxicosis
- Small goiters
- Fear of isotopes



Thioamides

Methimazole, Propylthiouracil (PTU)

Adverse Effects

- Nausea, dyspepsia
- Acute liver failure (PTU; 1/1000 patients)
- Pruritus, allergic dermatitis
- Agranulocytosis (~ 90 days)
- Pancytopenia

- Methimazole avoided in 1st trimester pregnancy (risk of embryopathy)
- PTU avoided rest or pregnancy due to risk of liver failure



Radioactive Iodine

131 lodine

Mechanism of Action

Radiation-induced destruction of thyroid parenchyma



Radioactive Iodine

131 lodine

Indications

- Graves disease
- Toxic nodule
- Toxic goiter
- Thyroid cancer (adjuvant therapy)



Radioactive Iodine

131 lodine

Adverse Effects

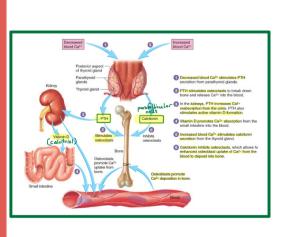
- Sore throat
- Hypothyroidism (long-term)

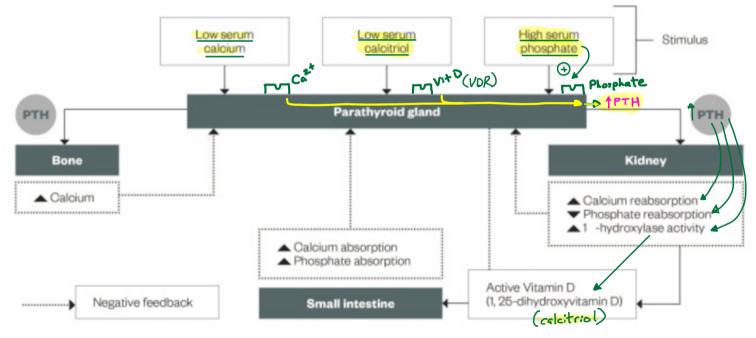
- Pregnancy
- Breastfeeding
- Uncontrolled thyrotoxicosis



Calcium Metabolism, Parathyroid, Bones

Normal Parathyroid Regulation





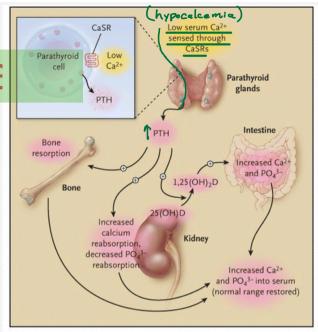
Calcium-Sensing Receptor Mime

(Calcimimetics)

Cinacalcet, etelcalcetide (IV)
(PO)

Mechanism of Action

- Binds CaSR on parathyroid cells
 - ↑ sensitivity of CaSR to extracellular Ca²⁺
 - Lower Ca²⁺ concentration at which PTH secretion is suppressed
 - ◆ Serum calcium and phosphorus



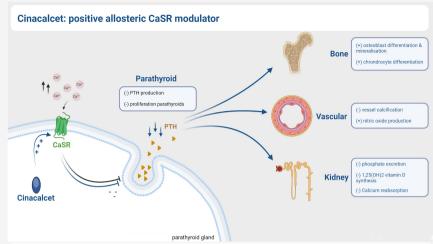


Calcium-Sensing Receptor

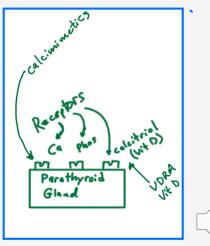
Cinacalcet, etelcalcetide

Indications

- Secondary hyperparathyroidism in CKD
- Parathyroid carcinoma
- Primary hyperparathyroidism (non-surgical candidates)



 Cinacalcet is a calcimimetic agent that increases sensitivity of the calcium-sensing receptors (CaSR) in the parathyroid gland to calcium → inhibiting release of PTH





Calcium-Sensing Receptor Mimetics

Cinacalcet, etelcalcetide —> 5 mg IV 3 times per week post-hemodialysis Cinacalcet (Sensipar) —> 30 mg PO daily or BID

Prescribing for Hyperparathyroidism with mild Hypercalcemia

- 15 mg PO
- Increase dose every 2 weeks
- Requires monitoring serum calcium and phosphorus levels weekly
- PTH measured within 4 weeks of initiation therapy and changing dosage



Calcium-Sensing Receptor Mimetics

Cinacalcet, etelcalcetide

Adverse Effects

- Hypocalcemia symptoms (eg, paresthesias, cramps)
- Malaise, myalgias
- Nausea, vomiting

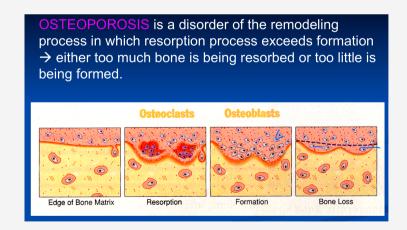
- Serum calcium below normal
- History of seizures (relative caution)
 - In patients with seizure disorders, seizure threshold is lowered with significant reduction in serum calcium levels.



Zoledronic acid (IV), Pamidronate (IV), Alendronate (PO weekly), Risedronate (PO monthly), Ibadronate (PO monthly) (Zometa) (Aredia) (Fosamax)

Mechanism of Action

- Inhibit osteoclast activity
- Inhibitor of bone resorption



Biphoshonate: Alendronate (Fosamax)

Mechanism of Action: Alendronate concentrates in mineral tissue and interfere with osteoclast-medicated bone resorption → increases BMD

Indication: Alendronate is considered 1st line therapy for prevention and treatment of osteoporosis in postmenopausal women due to its efficacy and low side effect profile

Side Effects: GI symptoms → acid regurgitation

 Alendronate is taken with 6-8 oz of water 30 mins before breakfast, in an upright position

Zoledronic acid (IV), Pamidronate (IV), Alendronate (PO weekly), Risedronate (PO monthly), Ibadronate (PO monthly)

Indications

- Osteoporosis (postmenopausal, GC induced)
- Paget disease
- Hypercalcemia
- Hyperparathyroidism

Paget disease of bone (PDB), which is characterized by an accelerated rate of bone remodeling resulting in overgrowth of bone at selected sites and impaired integrity of affected bone, is believed to be a disease of the osteoclast.

Paget is characterized by an accelerated rate of bone remodeling, resulting in overgrowth of bone at selected sites and impaired integrity of affected bone. The main clinical manifestations are pain and deformities in affected areas and a heightened risk of fracture, although many patients are asymptomatic. Osteoarthritis in nearby joints and neurologic disease are common complications, and the vascularity of pagetic bone may result in excessive bleeding during orthopedic surgery on affected areas.

Treatment with bisphosphonates, such as zoledronic acid, risedronate, and alendronate, can usually ease pain, slow bone turnover, and promote deposition of normal lamellar bone, which in turn results over time in the normalization of serum alkaline phosphatase and other markers of bone turnover and may lead to radiographic healing of lytic lesions. However, alternative agents, such as calcitonin, are sometimes required in patients unable to use these bisphosphonates. Analgesic, rehabilitative, surgical, and other measures may also be of benefit.

Zoledronic acid (IV), Pamidronate (IV), Alendronate (PO weekly), Risedronate (PO monthly), Ibadronate (PO monthly)

Prescribing

- Administered in the morning, 40 minutes prior to food consumption
- With at least 8 ounces of water
- Half-life of 10 years
- Re-check DXA in 3 years

Bone Density Axial Scan



Zoledronic acid (IV), Pamidronate (IV), Alendronate (PO weekly), Risedronate (PO monthly), Ibadronate (PO monthly)

Adverse Effects

- Heartburn, esophagitis
- Abdominal pain, diarrhea
- Acute phase response (IV) –fever, chills, flushing, MSK pain
- Jaw necrosis (rare)

- CrCl below 35 ml/min
- Active GI disease (no oral formulations)



Selective Estrogen Receptor Modulators (SERMs)

Raloxifene, tamoxifen

Mechanism of Action

- Bind estrogen receptors
- Agonist effect on bone → increase BMD
- Antagonist effect on breast → ↓ cancer risk

Raloxifene (Avista)

Raloxifene is a SERM (selective estrogen receptor modulator) with agonist and antagonist properties

Mechanism of Action:

- 1. Raloxifene binds to estrogen receptors as an <u>agonist</u> in bone and lipid metabolism
 - → inhibits osteoclasts → decreases bone resorption
 - → increases BMD (bone mineral density)
- 2. Raloxifene binds to estrogen receptors as an <u>antagonist</u> in breast and endometrial tissue
 - --> decreases risk of breast and uterine cancers
- Antagonist effect on endometrium (tamoxifen) → ↓ cancer risk



SERMs

Raloxifene, tamoxifen

Indications

Raloxifene (Avista)

- Dose: Raloxifene (Avista) 60 mg PO daily.
- Efficacy / Indication: Studies have demonstrated that Raloxifene is not as effective as Alendronate (Fosamax) for increasing BMD (4.8% vs. 2.2%).

- Patients with active venous thromboembolism (VTE) or a past medical history of VTE
- Women who are pregnant, plan to become pregnant, and those nursing (i.e., lactation)
- Prevention and treatment of postmenopausal osteoporosis
- Breast cancer prevention in high-risk women
- Alternative to bisphosphonates when contraindicated

SERMs

Raloxifene, tamoxifen

Adverse Effects

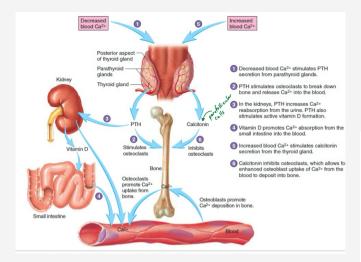
- Hot flashes
- Increased risk of venous thromboembolism

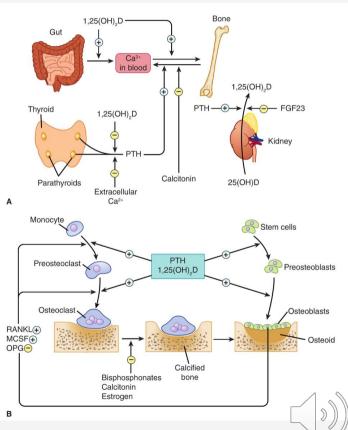
- Active or past VTE
- Pregnancy or breastfeeding
- Estrogen-dependent cancer (relative)
- Hepatic impairment



General

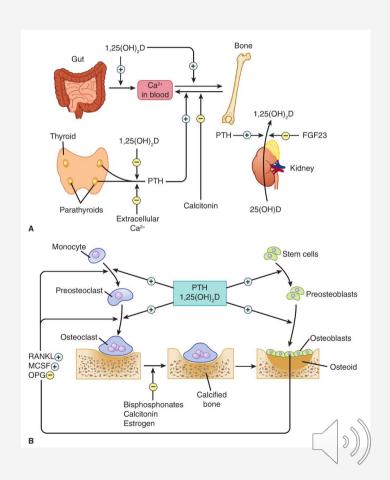
- Peptide hormone
- Secreted by thyroid gland
- Used where acute reductions in serum calcium needed
- Increases bone mass (but not as effective as bisphosphonates)





Mechanism of Action

- Binds to calcitonin receptors on osteoclasts
- Inhibits osteoclast activity → ↓ bone resorption
- Promotes renal calcium excretion
- ↓ serum calcium and phosphate



Indication

- Paget disease
- Hypercalcemia
- Postmenopausal osteoporosis



Adverse Effects

- Nausea, hand swelling
- Hypersensitivity reaction
- Flushing, urticaria
- Hypocalcemia (rare)

Contraindications

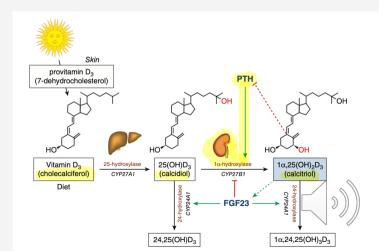
Hypocalcemia



Cholecalciferol, calcitriol, ergocalciferol

General

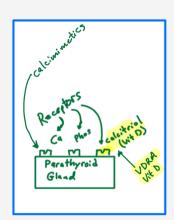
- Cholecalciferol (vitamin D3) PO & IV
- Calcitriol (1,25 dihydroxycholecalciferol) PO & IV
- Ergocalciferol (vitamin D2) PO



Cholecalciferol, calcitriol, ergocalciferol

Mechanism of Action

- Increases intestinal absorption of calcium and phosphate
- Promotes bone mineralization
- Suppresses PTH secretion (with adequate calcium)





Cholecalciferol, calcitriol, ergocalciferol

Indications

- Vitamin D deficiency or insufficiency (D3, D2)
- Osteoporosis and osteomalacia (D3, D2)
- Secondary hyperparathyroidism in CKD (calcitriol)
- Rickets in children (calcitriol)

Calcipenic rickets comprises a group of disorders in which supply of calcium or its intestinal absorption is too low to match the calcium demands imposed by bone growth.

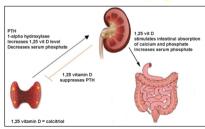
The most common cause of calcipenic rickets is dietary deficiency of vitamin D and/or calcium, resulting in an inadequate supply of calcium for bone mineralization. Alternatively, calcipenic rickets may be caused by decreased vitamin D activity (eg, lack of conversion to the active metabolite or resistance to the active metabolite) or secondary causes of reduced intestinal calcium absorption. Patients with calcipenic rickets usually have secondary hyperparathyroidism and characteristic changes of the growth plates and metaphyseal bone.

Treatment of Secondary Hyperparathyroidism (SHPT)

Vit D receptor agonists (VDRA), Vit D analogues, and calcimimetics are all considered 1st line options for lowering PTH in CKD stage 5D; and, the choice of which agent to use should be guided by serum levels of calcium, phosphate, and PTH.

Vitamin D Receptor Agonist (VDRA): Calcitriol (Rocaltrol)

- Calcitriol (1,25-dihydoxyvitamin D) is the active form of vitamin D synthesized in the kidney
 → interacts with Vit D receptors (VDR) in parathyroid, intestines, bone, and kidney.
- As a vit D receptor agonist (VDRA), calcitriol binds to vit D receptors (VDR) on the parathyroid gland and prevents SHPT by inhibiting PTH secretion.
- Note: Calcitriol also binds to VDR in the GI tract to stimulate absorption of calcium and phosphorus. Therefore, it is important to control serum phosphorus and calcium levels in patients with CKD-MBD before using calcitriol, since



hypercalcemia and elevated phosphorus levels may be detrimental to vascular tissue.

Calcitrol is available as an oral formulation (Rocaltrol) or IV formulation (Calcilex) with

 Calcitriol is available as an oral formulation (Rocaltrol) or IV formulation (Calcijex) with usual doses of 0.25-0.5 mcg/day.

Cholecalciferol, calcitriol, ergocalciferol

Adverse Effects

- Hypercalcemia
- Hypercalciuria
- Nausea, vomiting, constipation
- Kidney stones (rare)

- Hypercalcemia
- Vitamin D toxicity (hypervitaminosis
 D)



Calcium supplementation Dietary Reference Intakes for Calcium and Vitamin D³³

Mechanism of Action

- Replaces dietary deficiency
- Essential mineral for neuromuscular function
- Needed for bone mineralization

D					
Males					
g)					
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g)a					

^aNOF recommends vitamin D 800 to 1,000 IU in patients ≥ 50 years. IU, International Unit; RDA, Recommended Dietary Allowance.

CALCIUM SUPPLEMENTS					
<u>SUPPLEMENT</u>	ELEMENTAL CALCIUM				
Calcium Carbonate	40 %				
Calcium Lactate	13 %				
Calcium Gluconate	9 %				
Calcium Citrate	21 %				
Calcium Phosphate	39 %				
Calcium Glubionate	6.5 %				

Calcium supplementation

Indication

- Hypocalcemia
- Osteoporosis prevention/treatment
- Calcium deficiency from diet or malabsorption



Calcium supplementation

Adverse Effects

- Constipation
- Hypercalcemia with excessive intake
- Kidney stones (especially with high vitamin D)
- Gl upset

- Hypercalcemia
- Renal calculi history
- Severe renal impairment



Sex Hormone Related Drugs



Testosterone, Testosterone Esters, 17-alpha Alkylated Androgens (oxandrolone, stanozolol)

General

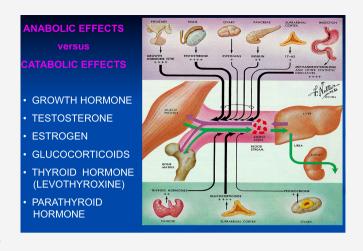
- Androgens are produced in testis, adrenal and ovary
- Synthesized from progesterone and dehydroepiandrosterone (DHEA)



Testosterone, Testosterone Esters, 17-alpha Alkylated Androgens

Mechanism of Action

- Androgens enter cells and bind cytosol receptors
- Hormone-receptor enters nucleus & modulates expression of target genes
- Stimulates protein synthesis, muscle, and bone mass -> and bolic property
- Promotes secondary sex characteristics -> androgenic property



Testosterone, Testosterone Esters, 17-alpha Alkylated Androgens

Indications

- Primary or secondary hypogonadism in males
- Delayed puberty (selected cases)
- Hormone therapy in transgender men



Testosterone, Testosterone Esters, 17-alpha Alkylated Androgens

Adverse Effects

- Acne and oily skin
- Erythrocytosis
- Virilization in females
 (hirsutism, enlarged clitoris, deepened voice) in females
- Feminization in males
 (gynecomastia, testicular atrophy,
 infertility)

- Prostate or breast cancer
- Untreated sleep apnea.
- Polycythemia
- Desire to preserve fertility
 - · Testosterone stimulates spermatogenesis.
 - Testosterone replacement therapy (TRT) can
 potentially worsen OSA symptoms by increasing
 upper airway resistance and decreasing muscle tone
 in upper airway dilator muscles, which are
 responsible for keeping the airway open during sleep.
 TRT an also increase metabolic requirements for
 oxygen, potentially worsening hypoxia during sleep.



General

- Considered a SERM
- Used in female infertility, especially PCOS
- Taken orally in short treatment cycles

Clomiphene citrate – Clomiphene citrate had been the first-line drug for this population for many years. However, clomiphene appears to be less effective for live birth rates than letrozole [52]. In women with PCOS, an ovulatory rate of 80 percent and a cumulative pregnancy rate of 30 to 40 percent can be expected. Cumulative pregnancy rate is dependent on patient BMI, with higher BMI levels associated with lower cumulative pregnancy rate

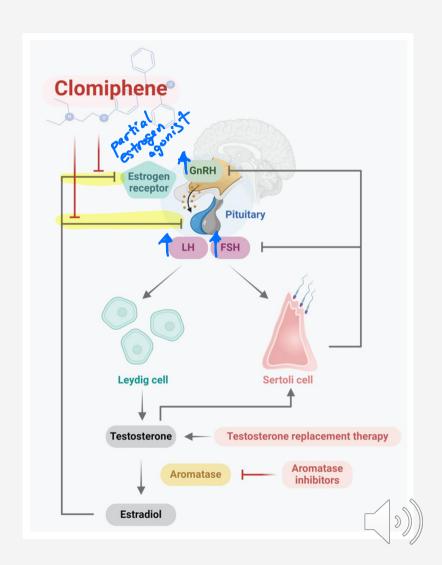
The polycystic ovary syndrome (PCOS) is an important cause of androgen excess, menstrual irregularity, and cardiometabolic dysfunction in women. When fully expressed, the manifestations include irregular menstrual cycles, hirsutism, obesity, insulin resistance, and anovulatory infertility.

Anovulation is a condition where the ovaries do not release an egg (ovulate) during a menstrual cycle.



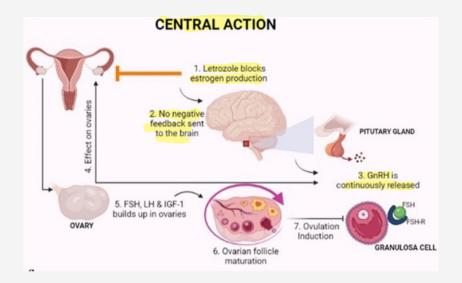
Mechanism of Action

- Partial estrogen R agonist at pituitary
- Blocks estrogen inhibitory actions on gonadotropin release
- Increases FSH and LH output
- Results in enlargement of ovaries and ovulation



Indications

- Ovulatory dysfunction (eg, PCOS)
- Female infertility





Adverse Effects

- Hot flashes
- Ovarian enlargement or cysts
- Multiple pregnancies

- Pregnancy
- Liver disease
- Uncontrolled adrenal or thyroid disorders
- Ovarian cyst unrelated to PCOS
- Abnormal uterine bleeding



Leuprolide, goserelin, histrelin, nafarelin, triptorelin

General

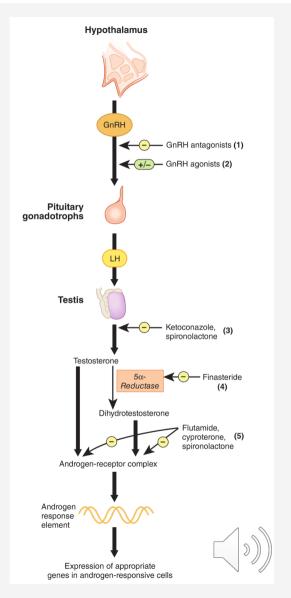
- GnRH stimulates gonadotropin release when secreted in pulsatile pattern by the hypothalamus
- Leuprolide synthetic peptides with long-acting GnRH agonist activity



Leuprolide, goserelin, histrelin, nafarelin, triptorelin

Mechanism of Action

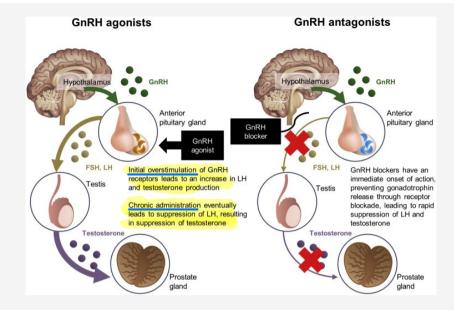
- Continuous stimulation by GnRH agonists → downregulation of GnRH receptors
 - ↓ LH and FSH secretion → ↓
 estrogen/testosterone
 - Initial surge followed by receptor downregulation



Leuprolide, goserelin, histrelin, nafarelin, triptorelin

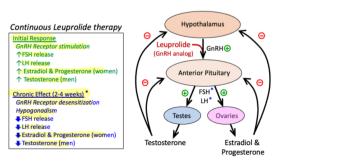
Indications

- Prostate cancer
- Endometriosis
- Uterine leiomyomata



Leuprolide

- Trade Name: Leuporn acetate, Lupron Depot ®
- Drug Class: GnRH agonist
- Mechanism:
- A synthetic analog of naturally occurring gonadotropin-releasing hormone (GnRH) that is resistant to peptidases involved in the
 enzymatic degredation of endogenous GnRH
- Produces an initial surge in release of LH & FSH, resulting in a transient increase in circulating gonadal steroids (testosterone in men, estradiol in premenopausal women).
- Continued administration over 2-4 weeks results in GnRH receptor desensitization, with resulting decrease in LH & FSH
 synthesis & secretion, with estradiol falling to postmenopausal concentration in women, and testosterone falling to "castrate
 levels" in men (Figure 1)(Fraser, 1993).



Leuprolide, goserelin, histrelin, nafarelin, triptorelin

Adverse Effects

- Hot flashes, night sweats
- Decreased libido, erectile dysfunction, gynecomastia (men)
- Bone loss (long-term use)

- Pregnancy
- Severe osteoporosis d/t + estrogen testosterone





References

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