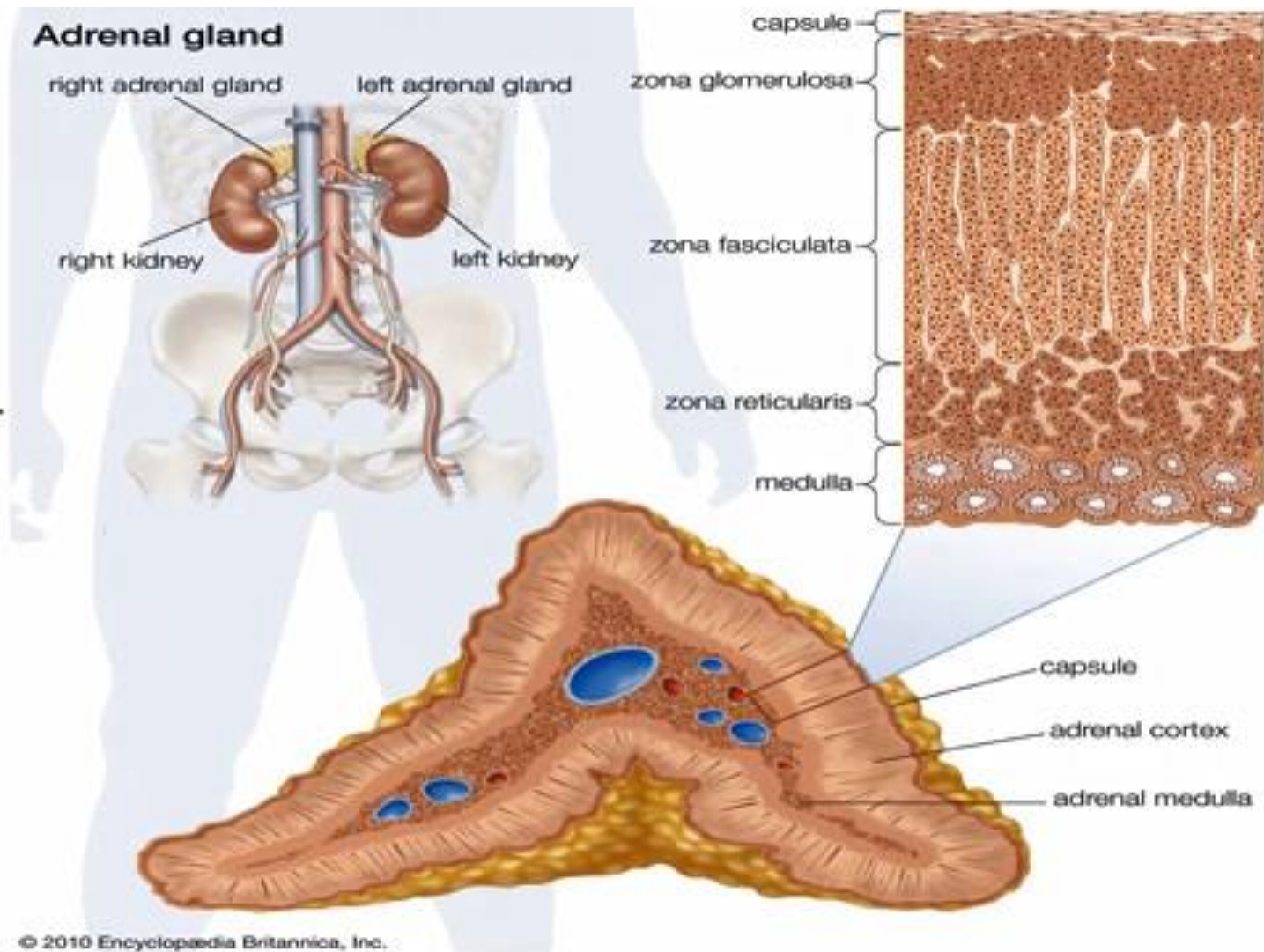
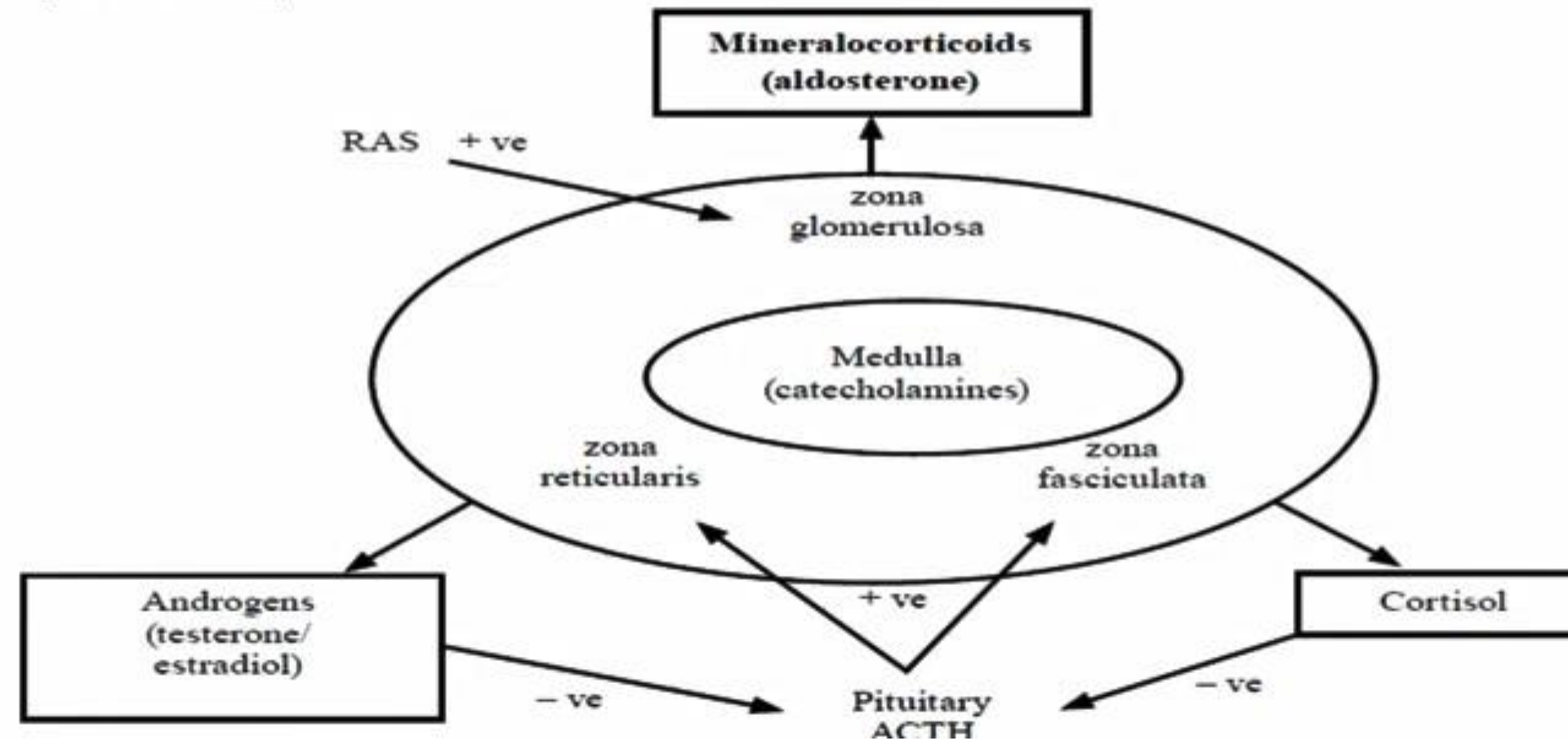
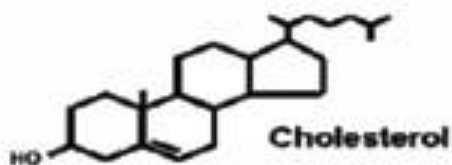


ENDOCRINE 4
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HYPERFUNCTION OF THE ADRENAL GLAND(Cushing syndrome)

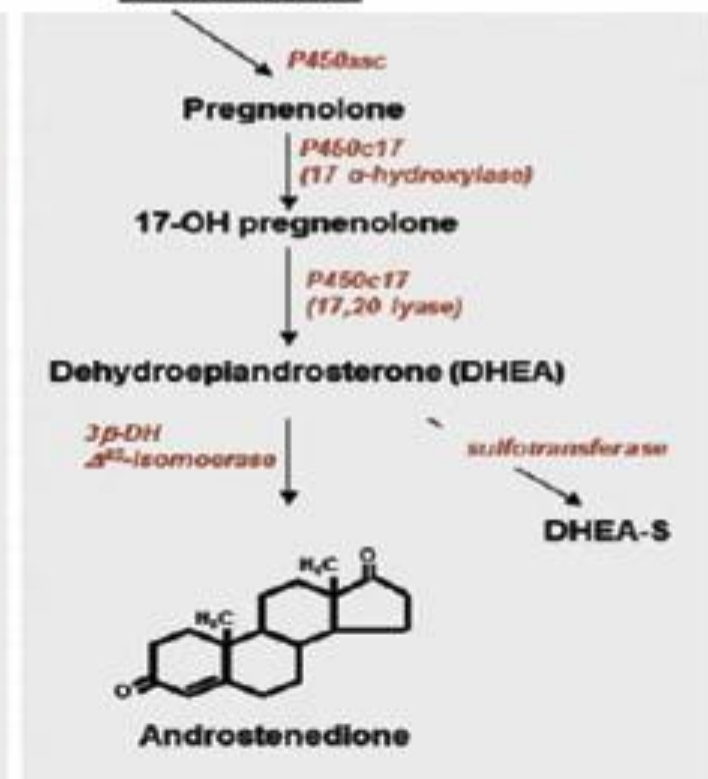
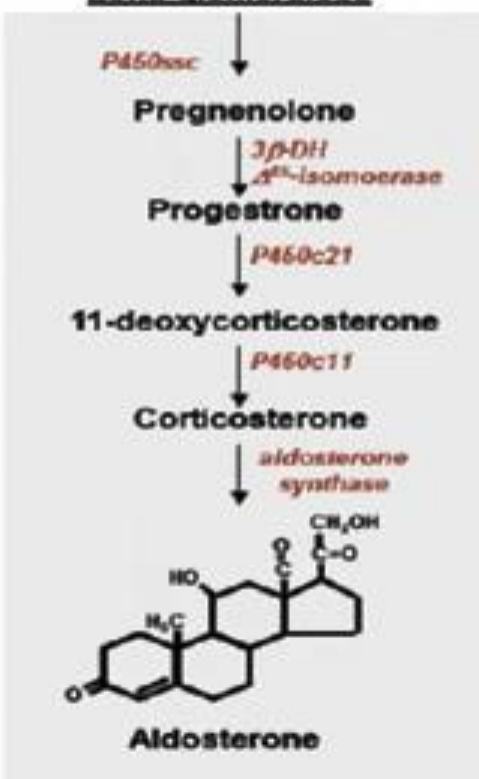
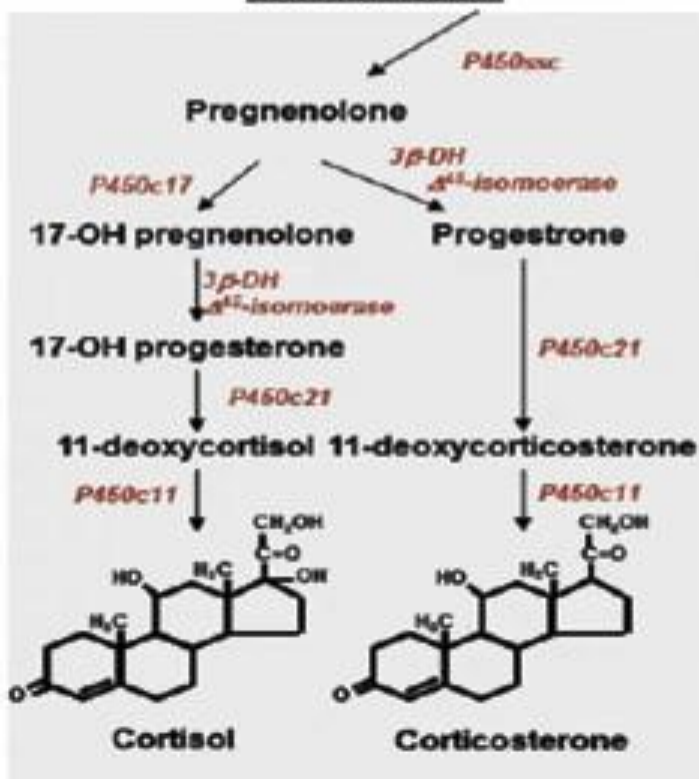




Zona fasciculata

Zona glomerulosa

Zona reticularis



Therapeutics

- If excessive exogenous corticosteroid use is causative, discontinue or minimize use.
- Surgical resection of causative area or tumor is usual treatment of choice.
- Pharmacotherapy is usually reserved on the basis of the same criteria listed earlier.

Possible
Treatment
Options in
Cushing
Syndrome
Based on
Etiology

Etiology	Treatment	
	Nondrug	Drug
Ectopic ACTH syndrome	Surgery, chemotherapy, irradiation	Metyrapone Ketoconazole
Pituitary-dependent	Surgery, irradiation	Mitotane Metyrapone Mifepristone Cabergoline Pasireotide
Adrenal adenoma	Surgery, postoperative replacement	Ketoconazole
Adrenal carcinoma	Surgery	Mitotane

Pharmacologic Therapy

Pharmacotherapy of Cushing syndrome can be divided into four categories

based on the anatomic site of action:

- (1) steroidogenesis inhibitors,
- (2) adrenolytic agents,
- (3) neuromodulators of ACTH release,
- (4) glucocorticoid-receptor blocking agents

drug selection is determined according to the etiology of Cushing syndrome, individual patient factors, and cost. Once the etiology has been correctly identified, patient sex and gender should be considered since some pharmacologic options (steroidogenesis inhibitors in particular) used in Cushing syndrome affect the sex hormones. Specifically, metyrapone is a clear second choice in women due to a high incidence of hirsutism, whereas ketoconazole may be a secondary choice in men due to drug induced gynecomastia and hypogonadism.

- During pregnancy, metyrapone is commonly used, while mifepristone must be voided. Additionally, women desiring pregnancy within the next 5 years should avoid mitotane as this agent is stored in adipose tissue for up to several years following discontinuation.
- Preexisting medication profiles should also be considered since many of the pharmacologic options can inhibit (eg, ketoconazole) or induce (eg, metyrapone) important CYP isoenzymes such as 3A4.

Drug	Adverse Drug Reaction	Monitoring Parameters	Comments
Cabergoline	Nausea, dizziness, headache, nasal congestion, constipation, psychiatric symptoms, valvulopathy	Echocardiogram	
Etomidate	Sedation, pain at injection site, hypotension, myoclonus, nausea, vomiting	Frequent sedation scoring initially, serum potassium, serum cortisol	
Ketoconazole	GI upset, dermatologic reactions; elevated hepatic transaminases, hepatotoxicity	Liver function tests, including ALT/AST, total bilirubin, ALP, prothrombin time, and INR testing	Approximately 10% will experience reversible LFT elevations
Metyrapone	Androgenic effects (hirsutism, acne, etc.), blood pressure and electrolyte abnormalities, nausea, vomiting, vertigo, headache, dizziness, abdominal discomfort, allergic rash	Blood pressure, electrolytes	
Mifepristone	Hypokalemia, nausea, fatigue, headache, peripheral edema, dizziness, endometrial hyperplasia	Serum potassium, pregnancy testing, pelvic ultrasound	Abortifacient; rule out pregnancy in women of childbearing potential
Mitotane	GI upset, nausea, diarrhea, lethargy, somnolence, CNS disturbances	UFC and urinary steroid production, serum potassium	GI upset in up to 80%; GI and CNS effects appear to be dose-dependent
Pasireotide	Nausea, diarrhea, cholelithiasis, increased hepatic transaminases, hyperglycemia, sinus bradycardia, QT prolongation	Serum glucose, serum potassium, hemoglobin A1c, liver function tests, UFC, thyroid function, heart rate, ECG	Only available as a subcutaneous injection; expensive

- **Steroidogenesis Inhibitors** block the production of cortisol. This class includes metyrapone, ketoconazole, and etomidate
- **Adrenolytic Agents** Mitotane is a cytotoxic drug that structurally resembles the insecticide dichlorodiphenyltrichloroethane (DDT). Mitotane inhibits the 11-hydroxylation of 11-desoxycortisol and 11-desoxycorticosterone in the adrenal cortex, resulting in an inhibition of cortisol and corticosterone synthesis
- **Neuromodulatory Agents** Pituitary secretion of ACTH is normally mediated by various neurotransmitters, including serotonin, γ -aminobutyric acid (GABA), acetylcholine, and the catecholamines
- Dopamine D2-receptor agonists, including bromocriptine and cabergoline, initially reduce ACTH secretion in as many as half of all patients with Cushing disease. This action occurs through activation of inhibitory D2 receptors that are expressed in approximately 80% of pituitary adenomas. Cabergoline exhibits a higher specificity and affinity for D2 receptors as well as a prolonged half-life compared with bromocriptine

- **The somatostatin analogs** octreotide and lanreotide generally are ineffective in reducing ACTH secretion in Cushing disease. These two agents primarily target somatostatin receptor subtype 2 (sst2), whereas pituitary adenomas predominantly express sst5. Pasireotide, a somatostatin analog, exhibits a high affinity for sst1, sst2, sst3, and, especially, sst5 receptor subtypes.
- Pasireotide is especially effective at normalizing UFC concentrations in patients whose baseline UFC is less than five times the upper limit of normal. Clinical signs and symptoms of Cushing disease are also improved as are blood pressure, weight, LDL cholesterol, and quality of life.
- Since coexpression of D2 and sst5 receptors is common in adrenocorticotropin-secreting adenomas, the combination of pasireotide and cabergoline may produce synergistic effects in reducing cortisol levels

- **Glucocorticoid-Receptor Blocking Agents**

- Mifepristone is a potent progesterone- and glucocorticoid-receptor antagonist
- mifepristone has an FDA-approved indication for treatment of endogenous Cushing syndrome in patients who have type 2 diabetes or glucose intolerance, and who are not eligible for or have had poor response to surgery.

Primary Aldosteronism

The most common causes of PA include bilateral adrenal hyperplasia (BAH) (65%) and aldosterone-producing adenoma (APA; otherwise known as Conn syndrome)

Aldosterone-receptor antagonists are the treatment of choice in BAH (Spironolactone)

Adverse effects of spironolactone are dose-dependent and include GI discomfort, impotence, gynecomastia, menstrual irregularities, and hyperkalemia.

Gynecomastia and menstrual irregularities observed with spironolactone therapy arise from activity at androgen and progesterone receptors and inhibition of testosterone biosynthesis

intolerant of spironolactone, alternative options include eplerenone and amiloride

HYPOFUNCTION OF THE ADRENAL GLAND (Addison disease)

Therapeutics

a. Steroid replacement (replace cortisol loss)

i. Oral administration is commonly dosed to mimic normal cortisol production circadian rhythm.

ii. Two-thirds administered in the morning and one-third in the evening

(a) This may cause periods of transient adrenal insufficiency or variable serum concentrations in some patients.

(b) Daily cortisol production in average patient: 5–10 mg/m²

b. Hydrocortisone: 15 mg/day (use may reduce need for fludrocortisone compared with use of cortisone or prednisone)

i. Cortisone acetate: 20 mg/day

ii. Prednisone: 2.5 mg/day

iii. Dexamethasone: 0.25–0.75 mg/day

c. Fludrocortisone (replaces loss of mineralocorticoid): 0.05–0.2 mg/day by mouth

Glucocorticosteroid	Relative Equivalent Dosing (mg)
Cortisone	25
Hydrocortisone	20
Prednisone	5
Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Dexamethasone	0.75

For women with decreased libido or low energy levels because of androgen deficiency, dehydroepiandrosterone:DHEA 25–50 mg/day

Note that during times of stress or illness, corticosteroid dosages must be increased. Dose and route of administration depend on level of stress to the body

ARACHIDONIC ACID

Cyclooxygenase Pathway

5- Lipoxygenase Pathway

Hydroperoxyeicosatetraenoic acid

5HPETE

COX-1 / COX-2

Prostaglandin G2 (PGG2)

Prostaglandin H2 (PGH2)

Tissue
specific
synthases

5HETE

Leukotriene B4

Leukotriene A4

Leukotriene C4

Leukotriene D4

Leukotriene E4

12-
Lipoxy
genase

Lipoxin A4

Lipoxin B4

@VijayPatho

PGD2

PGE2

PGF2 α

PGI2

TXA2

Prostacyclin

Thromboxane A2

Glucocorticoid	Anti-inflammatory Potency	Equivalent Potency (mg)	Approximate Half-Life (min)	Sodium-Retaining Potency
Cortisone	0.8	25	30	2
Hydrocortisone	1	20	90	2
Prednisone	3.5	5	60	1
Prednisolone	4	5	200	1
Triamcinolone	5	4	300	0
Methylprednisolone	5	4	180	0
Betamethasone	25	0.6	100-300	0
Dexamethasone	30	0.75	100-300	0

PITUITARY GLAND DISORDERS

- Acromegaly
- Treatment of choice is surgical resection of tumor
- Pharmacotherapy
- The primary treatment goals for patients diagnosed with acromegaly are to reduce GH and IGF-1 concentrations, improve the clinical signs and symptoms of the disease, and decrease mortality.
- biochemical control of acromegaly as suppression of GH concentrations to less than 1 mcg/L
- The most common pharmacologic treatment options include dopamine agonists, somatostatin analogs, and the GH-receptor antagonist pegvisomant.

Dopamine Agonists

In normal healthy adults, dopamine agonists cause an increase in GH production. However, when these agents are given to patients with acromegaly, there is a paradoxical decrease in GH production. The greatest clinical experience with the use of dopamine agonists in acromegaly has been **with bromocriptine or cabergoline**.

Dosing (**bromocriptine** is most commonly used agent)

(a) Initial: 1.25 mg/day by mouth

(b) Maximal: 20–30 mg/day (can titrate once or twice weekly, as needed)

Adverse effects

(a) Fatigue, dizziness, nervousness

(b) Diarrhea, abdominal pain

Efficacy: Normalization of IGF-1 concentrations in about 10% of patients. More than 50% of patients experience symptomatic relief.

Somatostatin Analogs

- Octreotide, lanreotide, and pasireotide are long-acting somatostatin analogs that are more potent in inhibiting GH secretion than endogenous somatostatin (40 times more potent than endogenous somatostatin). These agents also suppress the LH response to GnRH; decrease splanchnic blood flow; and inhibit secretion of insulin, vasoactive intestinal peptide (VIP), gastrin, secretin, motilin, serotonin, and pancreatic polypeptide. Pasireotide is a somatostatin analog that has a broader affinity for somatostatin receptor subtypes than octreotide or lanreotide and this may result in greater GH inhibition. Pasireotide is also effective for octreotide or lanreotide-resistant adenomas.
- A long-acting intramuscular formulation of octreotide (Sandostatin LAR) is available for monthly administration.
- Efficacy: 50%–60% of patients experience normalization of IGF-1 concentrations with good symptomatic relief as well. May shrink tumor mass in some patients

Growth Hormone Receptor Antagonist

Pegvisomat (Somavert) is a genetically engineered GH derivative that binds to, but does not activate, GH receptors and inhibits IGF-1 production. This agent is different from other medications used in the management of acromegaly because it does not inhibit GH production; rather, it blocks the physiologic effects of GH on target tissues. Therefore, GH concentrations remain elevated during therapy, and response to treatment is evidenced by a reduction in IGF-1 concentrations

Adverse effects

- (a) Nausea, vomiting
- (b) Flulike symptoms
- (c) Reversible elevations in hepatic transaminase

iv. Efficacy: More than 95% of patients attain normal IGF-1 concentrations, and most have improved symptoms.

Hyperprolactinemia

Treatment of choice is surgical resection of tumor, if causative

Pharmacotherapy usually reserved for:

- i. Control before surgery or irradiation
- ii. When surgery is not possible (usually requires lifelong pharmacotherapy)
- iii. Surgical failures or relapses after period of remission after surgery

Dopamine agonists

- i. Cabergoline (preferred agent according to the Endocrine Society guidelines, long-acting oral agent;

adverse effect profile similar to that for bromocriptine but fewer gastrointestinal [GI] adverse effects)

GH deficiency

Recombinant GH is currently considered the drug of choice for GHD short stature. GH replacement therapy in children with documented GHD short stature produces a significant improvement in growth velocity within the first year of therapy and significantly improves final adult height. The initial increase in growth velocity often is referred to as *catch-up growth*.