Pharmacology - 2

Dr. Yousef Abusamra. Ph.D.

Assistant professor of pharmacology and pharmacognosy

Faculty of Pharmacy

Philadelphia University – Amman - Jordan

yabusamra@philadelphia.edu.com

Pituitary Gland Hormones

Learning outcomes:

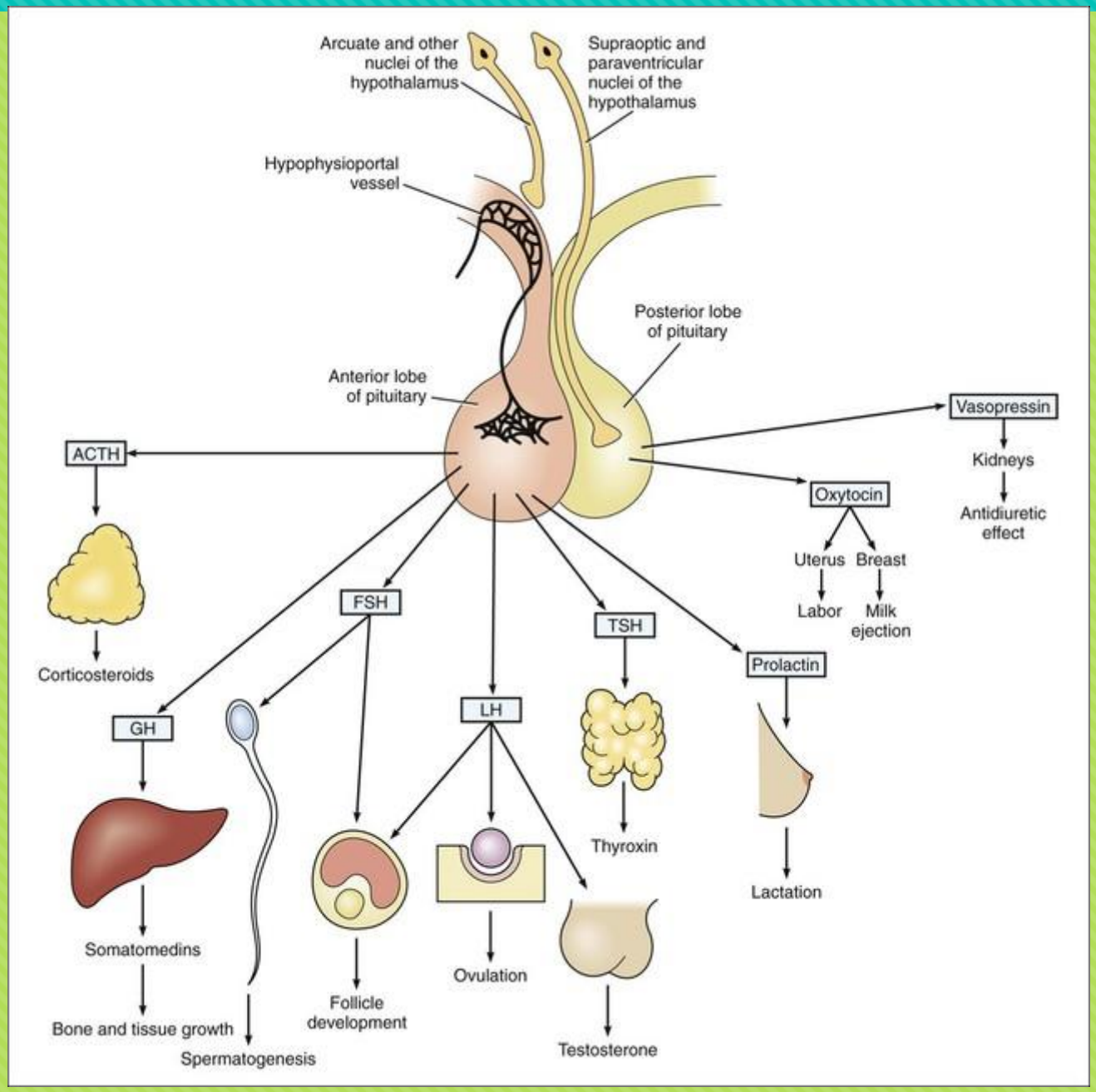
After studying this chapter, the student should be able to:

- List the hormones secreted by both lobes of the pituitary gland, their physiological effects and diseases related to their over-or undersecretion.
- Numerate the synthetic analogs of pituitary hormones, indications, side effects, precautions, interactions and important clinical considerations related to their use.
- Clarify the mechanisms of action of indicated drugs.
- List some of the drugs utilized in diseases characterized by the oversecretion of pituitary hormones, side effects of these drugs, precautions, interactions with other concomitantly administered agents and the prominent clinical considerations related to their use.

Pituitary Gland Hormones

- The control of metabolism, growth, and reproduction is mediated by a combination of neural and endocrine systems located in the hypothalamus and pituitary gland.
- The pituitary consists of an anterior lobe and a posterior lobe.
- It is connected to the overlying hypothalamus by a stalk of neurosecretory fibers and blood vessels.
- The posterior lobe hormones are synthesized in the hypothalamus and transported via the neurosecretory fibers in the stalk of the pituitary to the posterior lobe; from there they are released into the circulation.

Pituitary Gland Hormones



Pituitary Gland Hormones

Links between hypothalamic, anterior pituitary, and target organ hormone or mediator

Anterior Pituitary Hormone	Hypothalamic Hormone	Target Organ	Primary Target Organ Hormone or Mediator
Growth hormone (GH, somatotropin)	Growth hormone-releasing hormone (GHRH) (+), Somatostatin (–)	Liver, bone, muscle, kidney, and others	Insulin-like growth factor-I (IGF-I)
Thyroid-stimulating hormone (TSH)	Thyrotropin-releasing hormone (TRH) (+)	Thyroid	Thyroxine, triiodothyronine
Adrenocorticotropin (ACTH)	Corticotropin-releasing hormone (CRH) (+)	Adrenal cortex	Cortisol
Follicle-stimulating hormone (FSH) Luteinizing hormone (LH)	Gonadotropin-releasing hormone (GnRH) (+)[2]	Gonads	Estrogen, progesterone, testosterone
Prolactin (PRL)	Dopamine (–)	Breast	—

[1]All of these hormones act through G protein-coupled receptors except GH and PRL, which act through JAK/STAT receptors.

[2]Endogenous GnRH, which is released in pulses, stimulates LH and FSH release. When administered continuously as a drug, GnRH and its analogs inhibit LH and FSH release through down-regulation of GnRH receptors.

(+), stimulant; (–), inhibitor.

Hypothalamic & Pituitary Gland Hormones

ACTH	Adrenocorticotropic hormone (corticotropin)
CRH	Corticotropin-releasing hormone
FSH	Follicle-stimulating hormone
GH	Growth hormone
GHRH	Growth hormone–releasing hormone
GnRH	Gonadotropin-releasing hormone
hCG	Human chorionic gonadotropin
hMG	Human menopausal gonadotropin
IGF	Insulin-like growth factor
LH	Luteinizing hormone
PRL	Prolactin
rhGH	Recombinant human growth hormone
SST	Somatostatin
TRH	Thyrotropin-releasing hormone
TSH	Thyroid-stimulating hormone (thyrotropin)

Pituitary Gland Hormones

- Drugs that mimic or block the effects of hypothalamic and pituitary hormones have pharmacologic applications in three primary areas:

1. As **replacement** therapy for hormone deficiency states.
2. As **antagonists** for diseases caused by excess production of pituitary hormones;
3. As **diagnostic** tools for identifying several endocrine abnormalities.

- TSH, FSH, LH, and ACTH share similarities in the regulation of their release from the pituitary.
- Each is under the control of a distinctive hypothalamic peptide that stimulates their production by acting on G protein-coupled receptors.

Pituitary Gland Hormones

- **TSH** release is regulated by thyrotropin-releasing hormone (TRH).
- The release of **LH** and **FSH** (known collectively as gonadotropins) is stimulated by pulses of gonadotropin-releasing hormone (GnRH).
- **ACTH** release is stimulated by corticotropin-releasing hormone (CRH).
- An important regulatory feature shared by these four structurally related hormones is that they and their hypothalamic releasing factors are subject to feedback inhibitory regulation by the hormones whose production they control.
- **TSH** and **TRH** production is inhibited by the two key thyroid hormones, thyroxine and triiodothyronine.

Pituitary Gland Hormones

- Gonadotropin and GnRH production is inhibited in women by estrogen and progesterone, and in men by testosterone and other androgens.
- ACTH and CRH production are inhibited by cortisol.
- Feedback regulation is critical to the physiologic control of thyroid, adrenal cortical, and gonadal function and is also important in pharmacologic treatments that affect these systems.
- The hypothalamic hormonal control of GH and prolactin differs from the regulatory systems for TSH, FSH, LH, and ACTH.
- The hypothalamus secretes two hormones that regulate GH; growth hormone-releasing hormone (GHRH) stimulates GH production, whereas the peptide somatostatin (SST) inhibits GH production.

Pituitary Gland Hormones

- GH and its primary peripheral mediator, insulin-like growth factor-I (IGF-I), also provide feedback to inhibit GH release.
- Prolactin production is inhibited by the catecholamine dopamine acting through the D2 subtype of dopamine receptors.
- The hypothalamus does not produce a hormone that specifically stimulates prolactin secretion, although TRH can stimulate prolactin release, particularly when TRH concentrations are high in the setting of primary hypothyroidism.

Pituitary Gland Hormones

Hypothalamic Hormone	Clinical Uses
Growth hormone-releasing hormone (GHRH)	Used rarely as a diagnostic test for GH and GHRH sufficiency
Thyrotropin-releasing hormone (TRH, protirelin)	May be used to diagnose TRH or TSH deficiencies; not currently available for clinical use
Corticotropin-releasing hormone (CRH)	Used rarely to distinguish Cushing's disease from ectopic ACTH secretion
Gonadotropin-releasing hormone (GnRH)	May be used in pulses to treat infertility caused by GnRH deficiency Analogs used in long-acting formulations to inhibit gonadal function in children with precocious puberty, in some transgender/gender variant early pubertal adolescents (to block endogenous puberty), in men with prostate cancer and women undergoing assisted reproductive technology (ART) or women who require ovarian suppression for a gynecologic disorder
Dopamine	Dopamine agonists (eg, bromocriptine, cabergoline) used for treatment of hyperprolactinemia

Ectopic ACTH:

Increased ACTH due to non-pituitary factors (outside the pituitary gland)

GROWTH HORMONE (SOMATOTROPIN):

- Growth hormone, an **anterior** pituitary hormone, is required during **childhood and adolescence** for attainment of normal adult size and has important effects throughout postnatal life on lipid and carbohydrate metabolism, and on lean body mass and bone density.
- Its growth-promoting effects are primarily **mediated** via **IGF-I** (also known as somato**medin** C).
- **Somatropin** is the recombinant form of GH.
- Growth hormone mediates its effects via cell surface receptors of the JAK/STAT cytokine receptor superfamily.
- JAK/STAT (The Janus kinase/signal transducers and activators of transcription), The **JAK-STAT** signalling pathway is a chain of interactions between proteins in a cell, and is involved in processes such as **immunity, cell division, cell death** and **tumor formation**.

Pituitary Gland Hormones

USES:

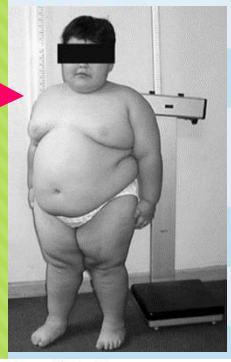
Prader-Willi syndrome is an autosomal dominant genetic disease associated with growth failure, obesity, and carbohydrate Intolerance.

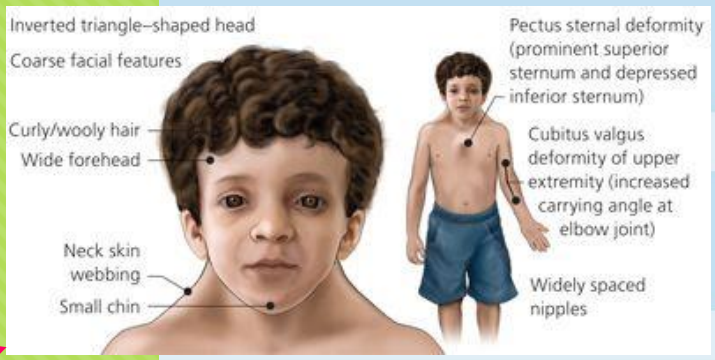
Turner syndrome:

Affects **girls**, short stature.

Noonan syndrome:

Unusual face characteristics, heart defects, development delays, malformations of bones





Primary Therapeutic Objective	Clinical Condition
Growth	Growth failure in pediatric patients associated with:
	Growth hormone deficiency
	Chronic renal insufficiency pre-transplant
	Noonan syndrome
	Prader-Willi syndrome
	Short stature homeobox-containing gene (SHOX) deficiency
	Turner syndrome
	Small-for-gestational-age with failure to catch up by age 2 years
	Idiopathic short stature
Improved metabolic state, increased lean body mass, sense of well-being	Growth hormone deficiency in adults
Increased lean body mass, weight, and physical endurance	Wasting in patients with HIV infection
Improved gastrointestinal function	Short bowel syndrome in patients who are also receiving specialized nutritional support

Toxicity:

- Hyperglycemia and pseudotumor cerebri.
- Increased risk of asphyxiation and otitis media.
- Pancreatitis and gynecomastia.
- Adults are subject to more side effects; Peripheral edema, myalgias, and arthralgias (soothe with decreased doses)

- Growth hormone treatment increases the activity of cytochrome P450 isoforms.

GROWTH HORMONE ANTAGONISTS:

- Oversecretion (from pituitary adenoma) of GH in adults results in acromegaly {abnormal growth of cartilage and bone tissue, and many organs including skin, muscle, heart, liver, and the gastrointestinal tract}.
- When a GH-secreting adenoma occurs before the long bone epiphyses close, it leads to a rare condition, gigantism.
- The initial therapy of choice for GH-secreting adenomas is endoscopic transsphenoidal surgery {performed through the nose to remove tumors from the pituitary gland and skull base}.
- Medical therapy with GH antagonists is introduced if GH hypersecretion persists after surgery.

- These agents include {1} **somatostatin analogs** and {2}**dopamine receptor agonists,** which reduce the production of GH, and the {3} novel GH receptor antagonist **pegvisoman** which prevents GH from activating GH signaling pathways.

Somatostatin analogs:

- Somatostatin has limited therapeutic usefulness because of its short duration of action and multiple effects in many secretory systems.
- **Octreotide**, the most widely used somatostatin analog.
- Octreotide, given subcutaneously every 8 hours, reduces symptoms caused by a variety of hormone-secreting tumors: acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, insulinoma, and ACTH-secreting tumor.

Lanreotide:

- A long-acting formulation of **lanreotide**, another octapeptide somatostatin analog, is approved for treatment of **acromegaly**.
- Lanreotide appears to have effects comparable to those of octreotide in reducing GH levels and normalizing IGF-I concentrations.

Pegvisomant:

- It is a GH receptor antagonist used to treat acromegaly.
- It is the polyethylene glycol (PEG, macrogol) derivative of a mutant GH.
- Pegylation (PEGylation) reduces its clearance and improves its overall clinical effectiveness.
- Pegvisomant does not inhibit GH secretion and may lead to increased GH levels and possible adenoma growth.

THE GONADOTROPINS (FOLLICLE-STIMULATING HORMONE & LUTEINIZING HORMONE) & HUMAN CHORIONIC GONADOTROPIN:

- In women, the principal function of FSH is to stimulate ovarian follicle development.
- Both FSH and LH are needed for ovarian steroidogenesis (sex hormones production, and other steroids,; estradiol and progesterone).
- In the ovary, LH stimulates androgen **production** in the follicular stage of the menstrual cycle.
- FSH stimulates the **conversion** of androgens to estrogens .
- In the luteal phase of the menstrual cycle, estrogen and progesterone production is primarily under the control first of LH and then, if pregnancy occurs, under the control of human chorionic gonadotropin (hCG).

- Human chorionic gonadotropin is a placental glycoprotein nearly identical with LH; its actions are mediated through LH receptors.
- In men, FSH is the primary regulator of spermatogenesis, whereas LH is the main stimulus for testosterone synthesis.
- FSH also stimulates the conversion of testosterone to estrogen that is also required for spermatogenesis.
- FSH, LH, and hCG are available in several pharmaceutical forms.
- They are used in states of **infertility** to stimulate spermatogenesis in men and to induce follicle development and ovulation in women.

Menotropins:

- A purified extract of FSH and LH extracted from the urine of postmenopausal women.
- Also known as human menopausal gonadotropins (hMG).

Urofollitropin:

- It is a purified preparation of human FSH extracted from the urine of postmenopausal women.
- Other preparations: **follitropin alfa** and **follitropin beta.**

Lutropin alfa:

- The first and only recombinant form of human LH.
- Lutropin has only been approved for use in combination with follitropin alfa for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency

Human Chorionic Gonadotropin:

- Human chorionic gonadotropin is produced by the human placenta and excreted into the urine, whence it can be extracted and purified.
- Choriogonadotropin alfa (rhCG) is a recombinant form of hCG.

CLINICAL USES OF GONADOTROPINS:

1. Ovulation induction.
2. Male infertility.
3. Chorionic gonadotropin is approved for the treatment of prepubertal {permanent} cryptorchidism {hidden testicle; one or both testicles being retained perpetually in the abdomen rather than lowering into the scrotum, which usually occurs by two months of age and always before six months of age}.
   - No longer used; surgical measure is preferred.

4. Chorionic gonadotropin has a **blackbox warning** against its use for **weight loss** (scientific research showed that this indication has no effect on obesity).

Suppression of gonadotropin production is indicated for:

1. Controlled ovarian stimulation: to prevent the production of multiple oocytes.
2. Endometriosis: the presence of estrogen-sensitive endometrium outside the uterus that results in cyclical abdominal pain in premenopausal women. The pain of endometriosis is often reduced by abolishing exposure to the cyclical changes in the concentrations of estrogen and progesterone.
3. Uterine leiomyomata (uterine fibroids): Uterine leiomyomata are benign, estrogen-sensitive, smooth muscle tumors in the uterus that can cause menorrhagia (heavy bleeding), with associated anemia and pelvic pain.

4. Prostate cancer: Androgen deprivation therapy is the primary medical therapy for prostate cancer.

5. Central precocious puberty: Continuous administration of a GnRH agonist is indicated for treatment of central precocious puberty (onset of secondary sex characteristics before 7–8 years in girls or 9 years in boys).

6. Advanced breast and ovarian cancer.

7. Recently, use of continuous GnRH **agonist** {either used to increase or decrease the release of GnRH} administration in early pubertal transgender adolescents to **block** endogenous puberty prior to subsequent treatment with cross-gender gonadal hormones.

GnRH RECEPTOR ANTAGONISTS:

- Ganirelix, cetrorelix, abarelix, and degarelix: are competitive antagonists of GnRH receptors.

PROLACTIN:

- Prolactin is the principal hormone responsible for lactation.
- It decreases sexual drive and reproductive function.
- A number of drugs elevate prolactin levels. These include antipsychotic and gastrointestinal motility drugs that are known dopamine receptor antagonists, estrogens, and opiates.
- There is no preparation available for hypoprolactinemic conditions.
- **Hyperprolactinemia** causes hypogonadism, which manifests with infertility, oligomenorrhea or amenorrhea, and galactorrhea in premenopausal women, and with loss of libido, erectile dysfunction, and infertility in men.
- Hyperprolactinemia is usually treated with **D2- receptor agonists** such as bromocriptine and cabergoline.

- These two agents are also used in the treatment of pituitary microadenomas, macroprolactinomas and hyperprolactinemia.

- The hypogonadism and infertility associated with hyperprolactinemia result from inhibition of GnRH release.

- For patients with symptomatic hyperprolactinemia, inhibition of prolactin secretion can be achieved with **dopamine agonists**, which act in the pituitary to inhibit prolactin release.

POSTERIOR PITUITARY HORMONES:

- In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, vasopressin and oxytocin, are not regulated by releasing hormones.
- In stead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals such as high plasma osmolarity and parturition (child birth).

OXYTOCIN:

- Oxytocin stimulates muscular contractions in the **uterus** and myoepithelial contractions in the **breast**.
- Thus, it is involved in parturition and the letdown of milk.
- During the second half of pregnancy, uterine smooth muscle shows an increase in the expression of oxytocin receptors and

….. becomes increasingly sensitive to the stimulant action of endogenous oxytocin.

- Oxytocin is administered intravenously for initiation and augmentation of labor.
- It also can be administered i.m. for control of postpartum bleeding.
- Oxytocin is **not** bound to plasma proteins and is rapidly eliminated by the **kidneys** and **liver**, with a circulating half-life of 5 minutes.
- Oxytocin also stimulates the release of prostaglandins and leukotrienes that augment uterine contraction.

- Oxytocin also causes contraction of myoepithelial cells surrounding mammary alveoli, which leads to milk letdown.
- Without oxytocin-induced contraction, normal lactation cannot occur.
- At high concentrations, oxytocin has weak antidiuretic and pressor activity due to activation of vasopressin receptors.

Toxicity & Contraindications:

- When oxytocin is used judiciously (calmly), serious toxicity is rare.
- The toxicity that does occur is due either to excessive stimulation of uterine contractions or to activation of vasopressin receptors.

Excessive stimulation of uterine contractions before delivery can cause fetal distress {birth asphyxia}, placental abruption {breaking}, or uterine rupture.

- High concentrations of oxytocin with activation of vasopressin receptors can cause excessive fluid retention, or water intoxication, leading to hyponatremia, heart failure, seizures, and death.
- Bolus injections of oxytocin can cause hypotension.

OXYTOCIN ANTAGONIST:

Atosiban:

- Is an antagonist of the oxytocin receptor that has been approved outside the United States as a treatment (**tocolysis**; anti-contraction, e.g. β-adrenoceptor agonists, Ca-channel blockers, … etc.) for **preterm labor**.
- It is as effective as β-adrenoceptor agonists.

VASOPRESSIN (ANTIDIURETIC HORMONE, ADH):

- It is structurally related to oxytocin.
- It is released in response to falling blood pressure.
- It possesses antidiuretic and vasopressor properties.
- A deficiency of this hormone results in **diabetes insipidus**.
- Vasopressin and desmopressin are treatments of choice for pituitary diabetes insipidus.
- Desmopressin acetate is a long-acting synthetic analog of vasopressin with minimal pressor activity and an antidiuretic-to-pressor ratio 4000 times that of vasopressin.
- Desmopressin can be administered intravenously, subcutaneously, intranasally, or orally.

Clinical pharmacology (indications):

- Vasopressin and desmopressin for pituitary diabetes insipidus.
- Desmopressin: nocturnal enuresis by decreasing nocturnal urine production.
- Vasopressin: esophageal variceal (of veins) bleeding (at lower esophagus) and colonic diverticular (of sacks) bleeding.
- High-dose vasopressin as a 40-unit intravenous bolus injection may be given to replace epinephrine in the Advanced Cardiovascular Life Support (ACLS) resuscitation protocol for pulseless arrest.
- Desmopressin is also used for the treatment of coagulopathy in hemophilia A and von Willebrand disease {a blood disorder in which the blood does not **clot** properly}.

Toxicity & Contraindications:

- Headache, nausea, abdominal cramps, agitation, and allergic reactions occur rarely.
- Overdosage can result in hyponatremia and seizures.
- Vasopressin (but not desmopressin) can cause vasoconstriction and should be used cautiously in patients with coronary artery disease.
- Nasal desmopressin may be less effective when nasal congestion is present.

VASOPRESSIN ANTAGONISTS:

- Conivaptan (i.v.) and tolvaptan (oral).
- Both agents promoted the excretion of free water, relieved symptoms, and reduced objective signs of hyponatremia and heart failure.
- Tolvaptan treatment duration is limited to 30 days due to risk of hepatotoxicity, including life-threatening liver failure.

THE END

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